



US008173861B2

(12) **United States Patent**  
**Madsen et al.**

(10) **Patent No.:** **US 8,173,861 B2**  
(45) **Date of Patent:** **May 8, 2012**

(54) **TRANSGENIC PIG MODEL FOR A  
HEREDITARY NEURODEGENERATIVE  
AUTOSOMAL DOMINANT DISEASE**

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(\*) Notice: Subject to any disclaimer, the term of this  
patent is extended or adjusted under 35  
U.S.C. 154(b) by 0 days.

(21) Appl. No.: **12/298,974**

(22) PCT Filed: **Apr. 30, 2007**

(86) PCT No.: **PCT/DK2007/000204**

§ 371 (c)(1),

(2), (4) Date: **Mar. 26, 2009**

(87) PCT Pub. No.: **WO2007/124751**

PCT Pub. Date: **Nov. 8, 2007**

(65) **Prior Publication Data**

US 2009/0304595 A1 Dec. 10, 2009

#### **Related U.S. Application Data**

(60) Provisional application No. 60/796,196, filed on May  
1, 2006.

(51) **Int. Cl.**

**C12N 15/00** (2006.01)

**A01K 67/027** (2006.01)

**G01N 33/00** (2006.01)

(52) **U.S. Cl.** ..... **800/17; 800/3; 800/9; 800/12;  
800/25; 435/455**

(58) **Field of Classification Search** ..... None  
See application file for complete search history.

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(57) **ABSTRACT**

The present invention discloses a non-human animal model  
for a hereditary autosomal dominant disease. The non-human  
animal model expresses at least one phenotype associated  
with the disease and is obtained by a genetic determinant. The  
invention also relates to sperm cells and embryos comprising  
the genetic determinant for an autosomal dominant disease.  
Furthermore, methods for producing the non-human animal  
model, sperm cell, and embryos are disclosed.

**22 Claims, 39 Drawing Sheets**

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1     ATGGCGACGA AGGCCGTGTG TGTGCTGAAG GGCGACGGCC CGGTGCAGGG CACCATCTAC  
61     TTCGAGCTGA AGGGAGAGAA GACAGTGTTA GTAACGGGAA CCATTAAAGG ACTGGCTGAA  
121    GGTGATCATG GATTCCATGT CCATCAGTTT GGAGATAATA CACAAGGCTG TACCAGTGCA  
181    GGTCCTCACT TCAATCCTGA ATCCAAAAAA CATGGTGGGC CAAAGGATCA AGAGAGGCAC  
241    GTTGGAGACC TGGGCAATGT GACTGCTGGC AAAGATGGTG TGGCCACTGT GTACATCGAA  
301    GATTCTGTGA TCGCCCTCTC GGGAGACCAT TCCATCATTG GCCGCACAAT GGTGGTCCAT  
361    GAAAAACCAG ATGACTTGGG CAGAGGTGGA AATGAAGAAA GTACAAAGAC GGGAAATGCT  
421    GGAAGTCGTT TGGCCTGTGG TGTAAATTGGG ATCACCCAGT AA

**Fig. 1**

1      ATGGCGACGA AGGCCGTGTG TGTGCTGAAG GGCGACGGCC CGGTGCAGGG CACCATCTAC  
61      TTCGAGCTGA AGGGAGAGAA GACAGTGTTA GTAACGGGAA CCATTAAAGG ACTGGCTGAA  
121      GGTGATCATG GATTCCATGT CCATCAGTTT GGAGATAATA CACAAGGCTG TACCAGTGCA  
181      GGTCTCACT TCAATCCTGA ATCCAAAAA CATGGTGGGC CAAAGGATCA AGAGAGGCAC  
241      GTTGGAGACC TGGGCAATGT GACTGCTGGC AAAGATCGTG TGGCCACTGT GTACATCGAA  
301      GATTCTGTGA TCGCCCTCTC GGGAGACCAT TCCATCATTG GCCGCACAAT GGTGGTCCAT  
361      GAAAAACCAG ATGACTTGGG CAGAGGTGGA AATGAAGAAA GTACAAAGAC GGGAAATGCT  
421      GGAAGTCGTT TGGCCTGTGG TGTAAATGGG ATCACCCAGT AA

**Fig. 2**

M.musculus MAMKAVCVLKGDPVQGTIHFEQKASGEPVVLSGQITGLTEGQHGFHVHQYGDNTQGCTS 60  
R.norvegicus MAMKAVCVLKGDPVQGVIIHFEQKASGEPVVVSGQITGLTEGEHGFHVHQYGDNTQGCTT 60  
H.sapiens MATKAVCVLKGDPVQGIINFEQKESNGPVKVWGSIKGLTEGLHGFHVHEFGDNTAGCTS 60  
s.scrofa MATKAVCVLKGDPVQGTIYFELK-GEKTVLVTGTIKGLAEGDHGFHVHQFGDNTQGCTS 59  
\*\* \*\*\*\*\* \* \*\* \* . . \* : \* \*.\*\*:\*\* \*\*\*\*\*:\*\*\*\* \*\*:

M.musculus AGPHFNPHSKKHGGPADEERHVGDLGNVTAGKDG~~V~~ANVSIEDRVISLSGEHSIIGRTMVV 120  
R.norvegicus AGPHFNPHSKKHGGPADEERHVGDLGNVAAGKD~~G~~VANVSIEDRVISLSGEHSIIGRTMVV 120  
H.sapiens AGPHFNPLSRKHGGPKDEERHVGDLGNVTADKD~~G~~VADVSIEDSVISLSGDHCCIIGRTLTVV 120  
S.scrofa AGPHFNPESSKKHGGPKDQERHVGDLGNVTAGKDG~~V~~ATVYIEDSVIALSGDHSIIGRTMVV 119  
\*\*\*\*\* \*:\*\*\*\*\* \*:\*\*\*\*\*;\*.\*\*\*\*\* \* \*\*\* \*\*:\*\*\*:\*.\*\*\*\*\*:\*\*

M.musculus HEKQDDLKGKGNEESTKTGNAGSRLACGVIGIAQ 154  
R.norvegicus HEKQDDLKGKGNEESTKTGNAGSRLACGVIGIAQ 154  
H.sapiens HEKADDLGKGKGNEESTKTGNAGSRLACGVIGIAQ 154  
S.scrofa HEKPDDLGRGGNEESTKTGNAGSRLACGVIGITQ 153  
\*\*\* \*\*\*\*\*:\*\*\*\*\*.\*\*\*\*\*.\*\*\*\*\*.\*

Fig. 3

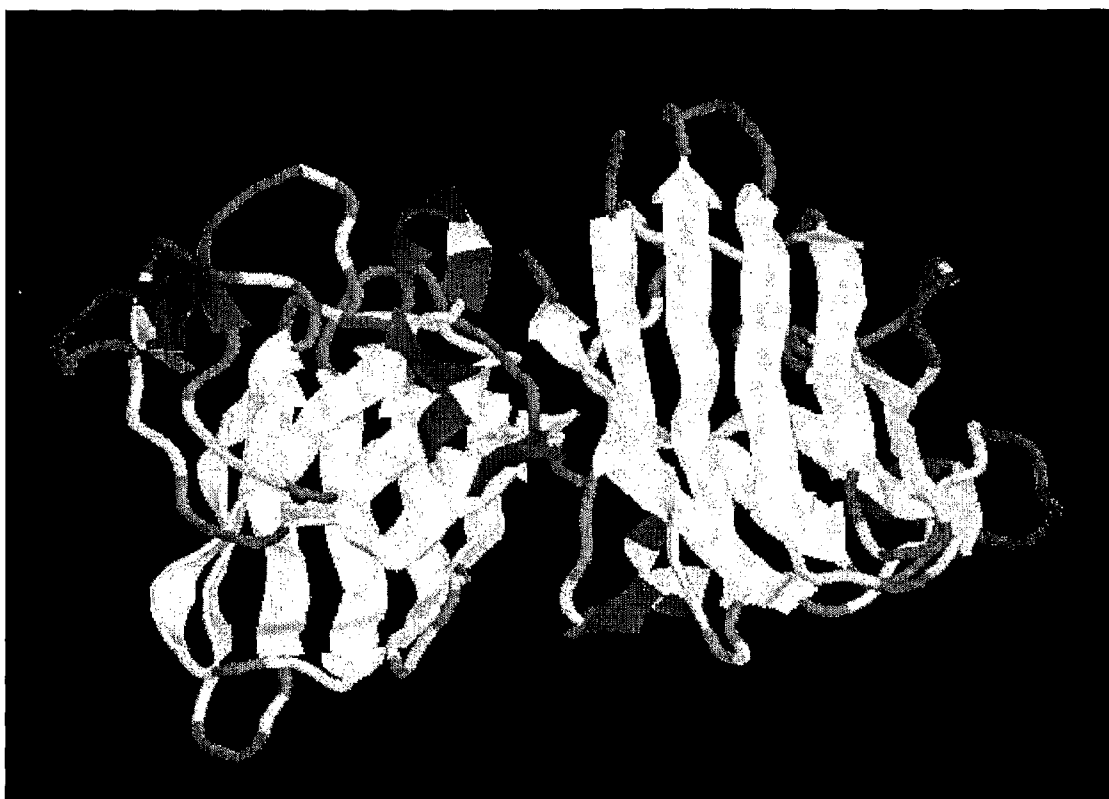


Fig. 4

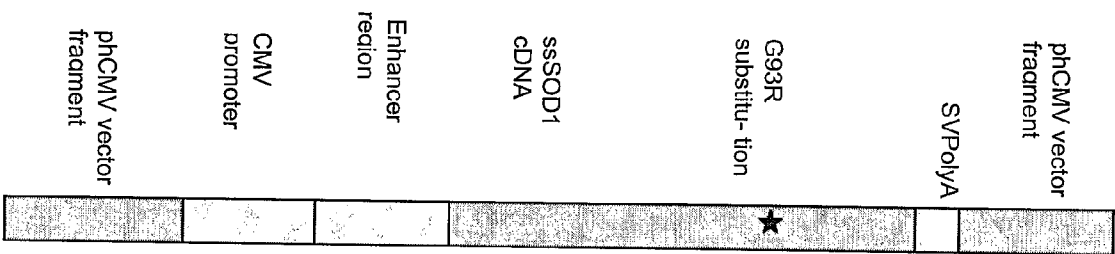
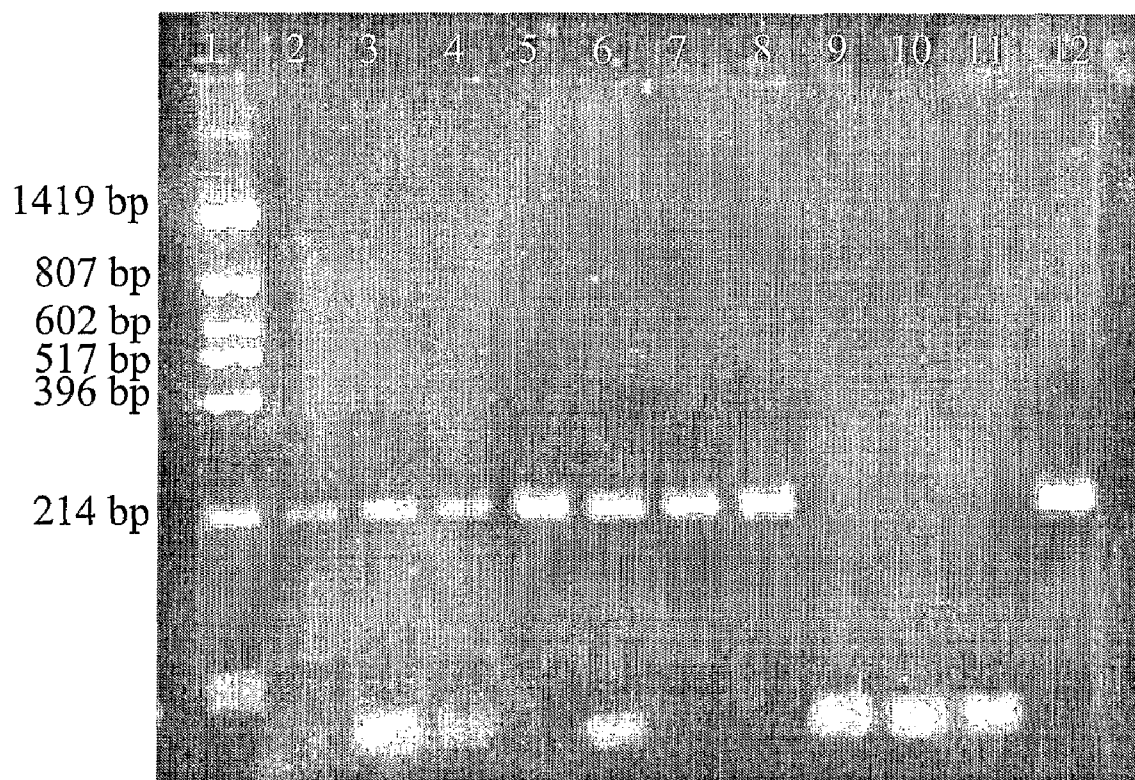


Fig. 5

**Fig. 6**

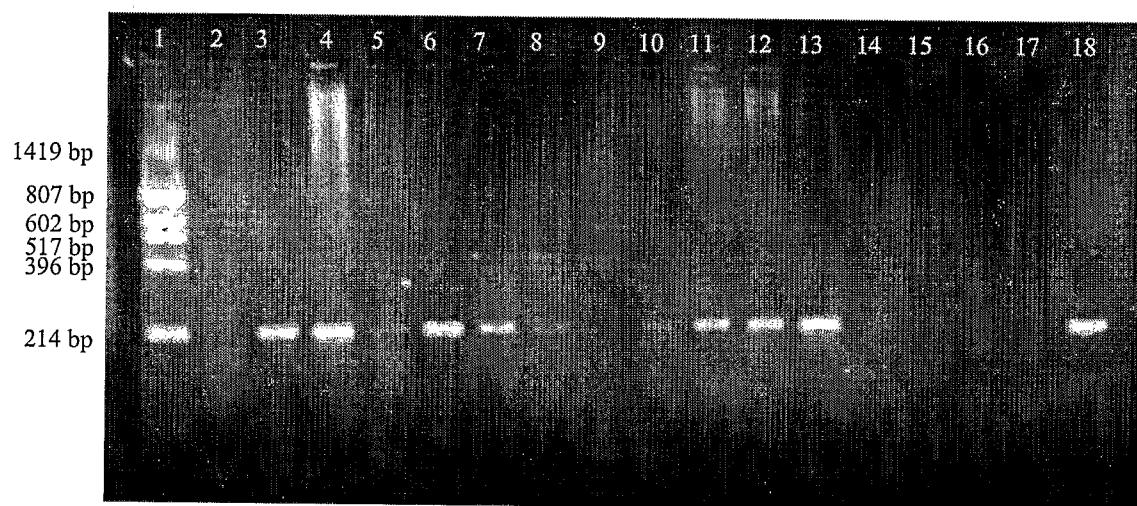
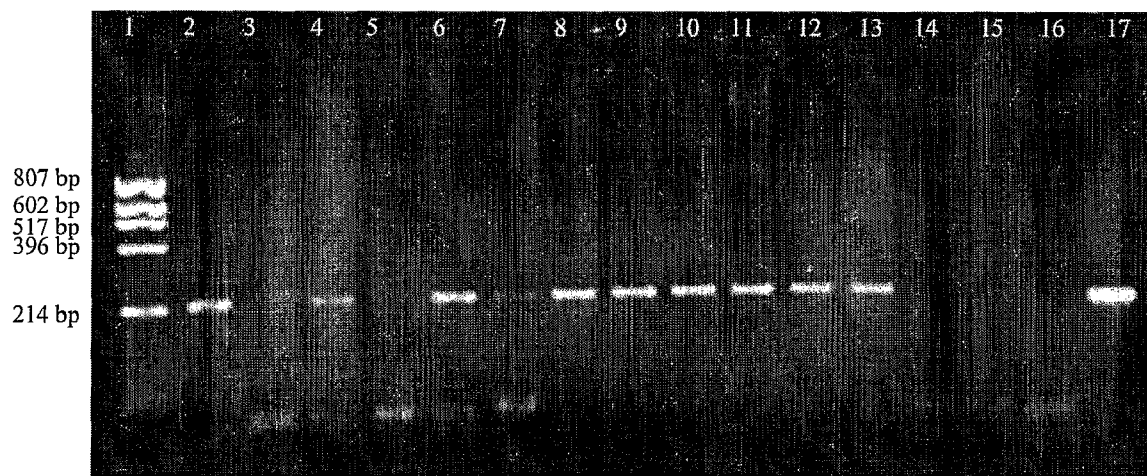


Fig. 7

**Fig. 8**

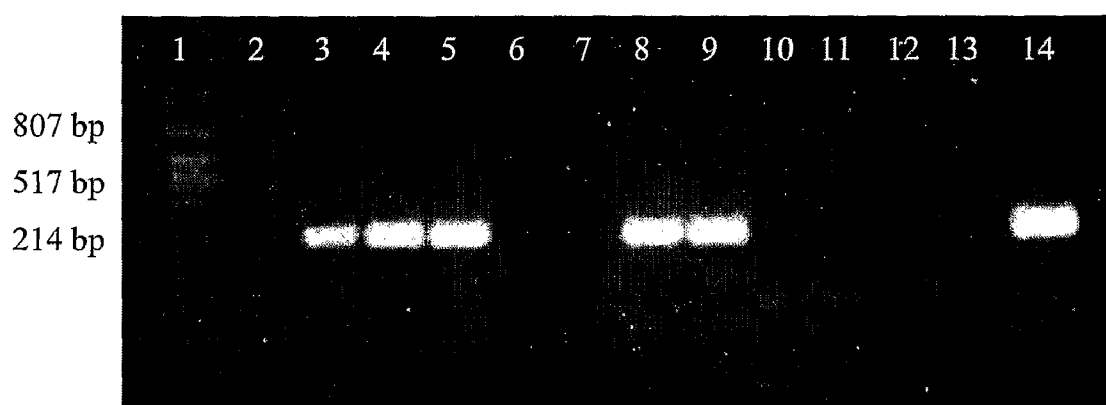


Fig. 9

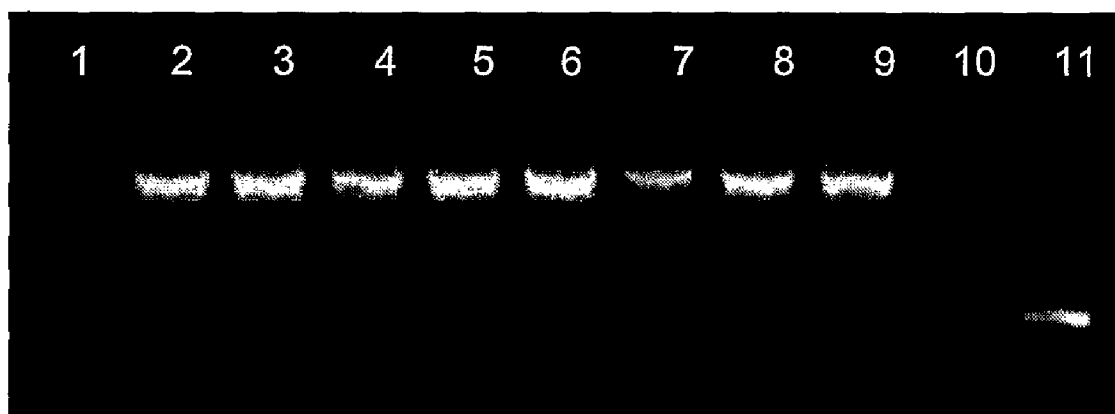


Fig. 10

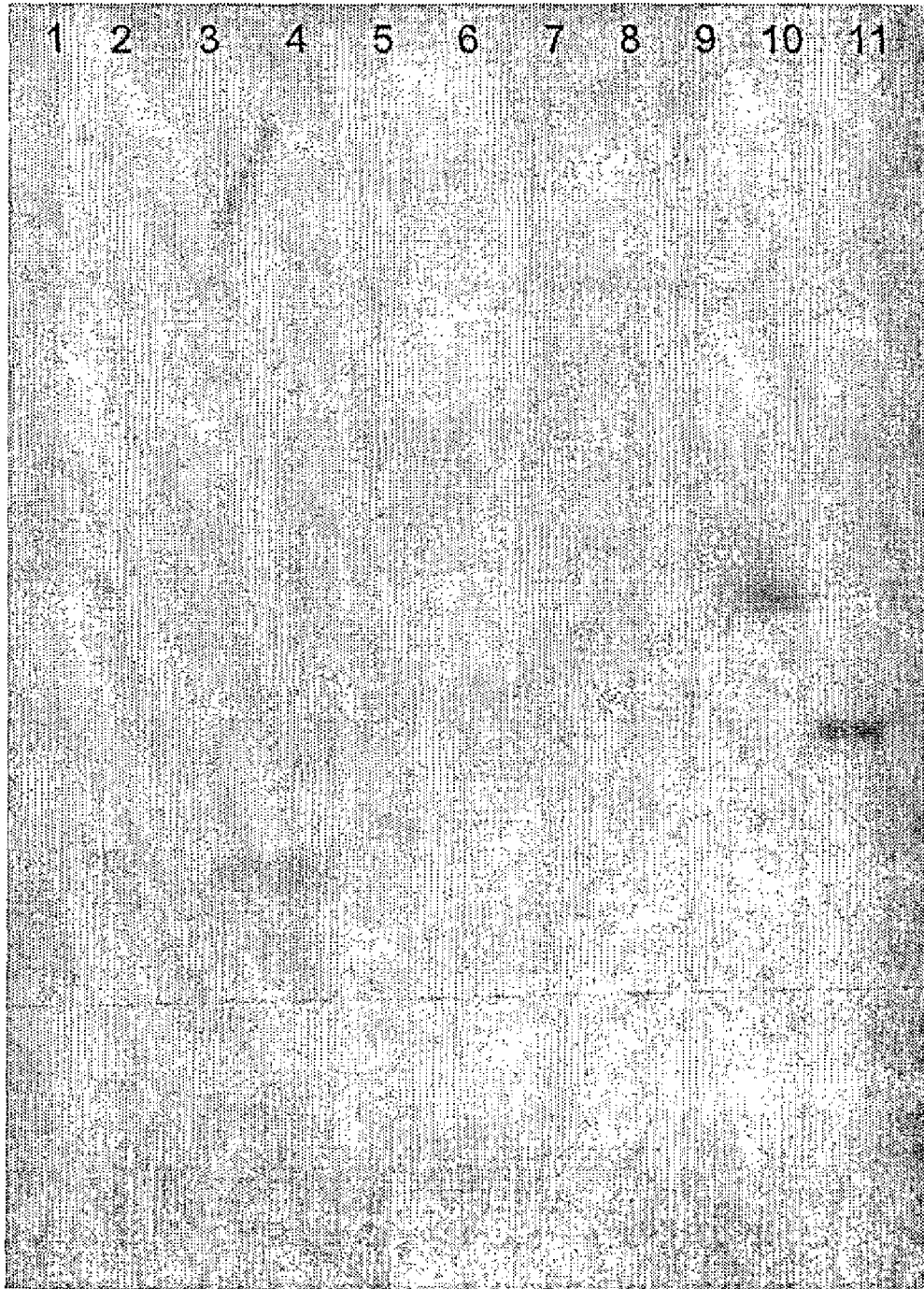


**Fig. 11**

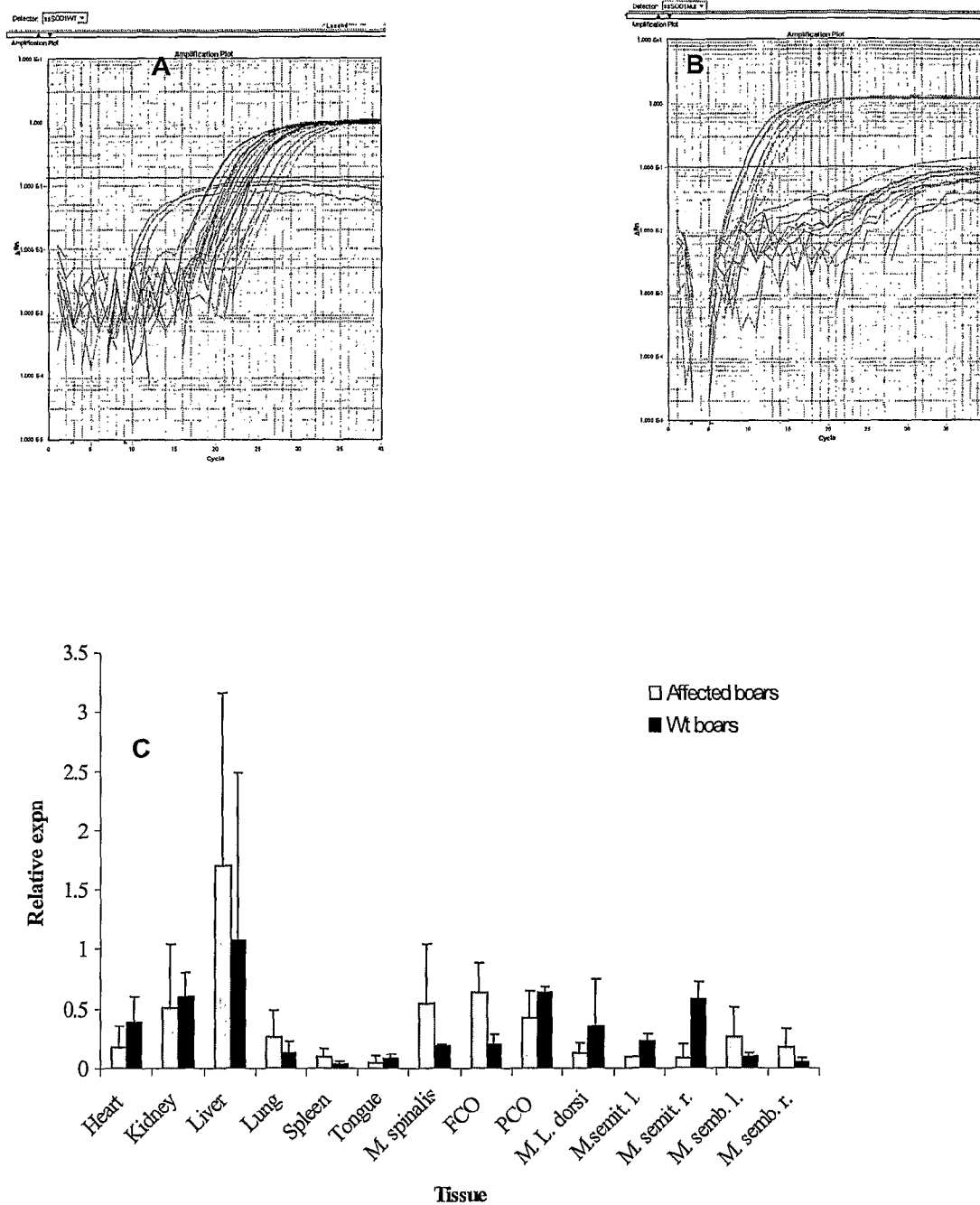


Fig. 12

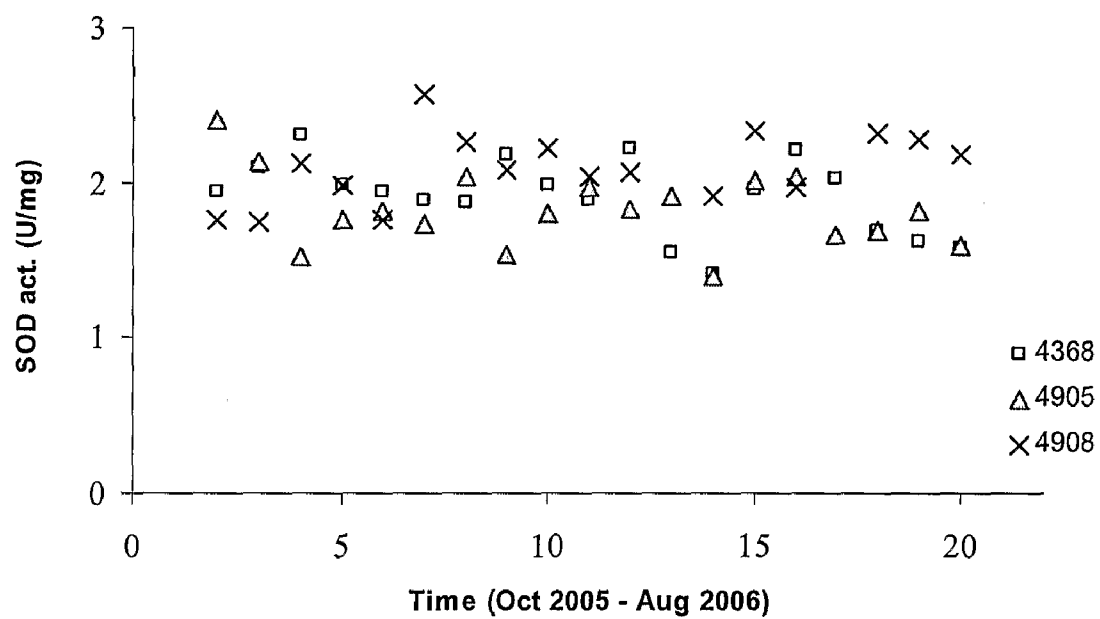


Fig. 13

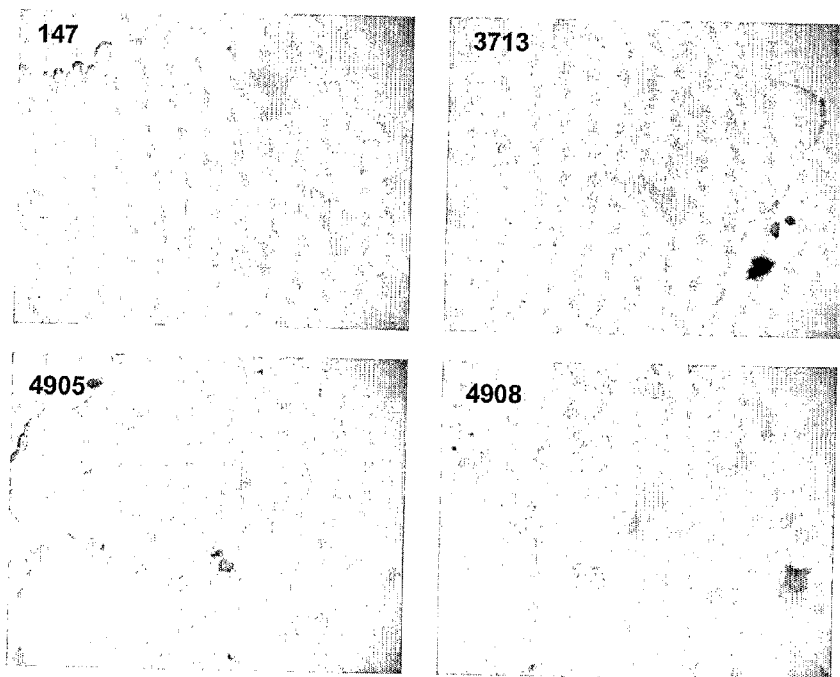
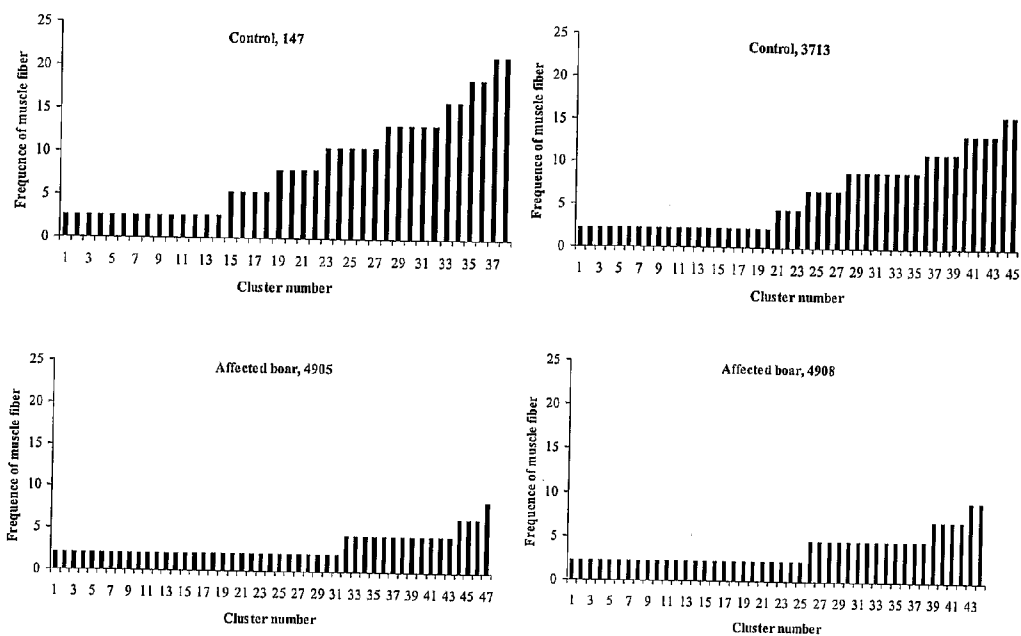


Fig. 14

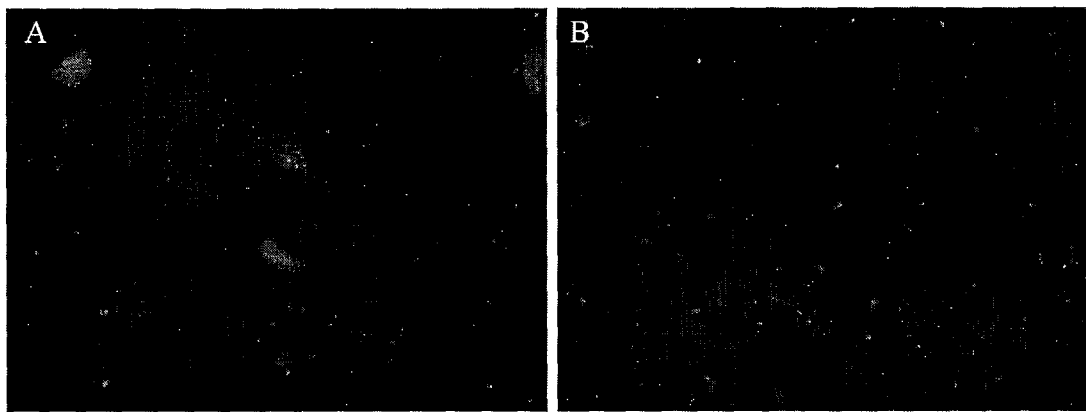


Fig. 15

```
1   cagtctgtta gggggaggag cttattttct cattccgggt tgatccagga acagctgttt
61  tccctccagc tctgaaagtg tggggtaaag gaattcatta gccatggatg tattcatgaa
121 aggactttca aaagccaagg agggagtctg ggctgctgct gaaaaacca aacaggggtgt
181 ggcagaagca gcgggaaaga caaaagaggg tgtgctctat gtaggatcca aaaccaagga
241 aggagtgggt catggtgtga caacagtggc tgagaagacc aaagagcaag tgacaaatgt
301 tggagaggca gtggtgacag ggggtgacag ggtagcacag aagacagtgg aaggagcagg
361 gagcattgca gctgccactg gctttggcaa aaaggatcag ctgggcaaga atgaagaagg
421 agccccccag gaggaattc tggaagatat gcctgtggat cctgacaatg aagcttatga
481 aatgccttcc gaggaagggg atcaggacta tgaaccggaa gcctaagggg tatctttgct
541 cccagtttcc tgagatctgc tgacagacgt gccatcctgt ccaagtgcc cgttcccacc
601 tgcccagtcg tgaccttctc tcaacgcttt cacagtgtct tttgaagtct tccatgagca
661 gtgactggag tatctgtacc cgccccacct cggttccggg gcttccctct cactgaatat
721 atggtagcag ggtcttgtgt gctgtggctg ttgtggcttc gaacctaaaa tgtttaatga
781 aaaacaccta agtgactacc acttatttct aaatctattt tttgttgctg ttgagaaatt
841 gtgagtgatt tactctccta agatttaaaa gtgtcttttc aggattccgt cgaagaataa
901 tgatgtatgg cgaaatttgt taatatatac aatacttaaa catgtgagca tggaaactatg
961 cacctataaa tattaactat ag
```

Fig. 16

↓

|               |                                                               |     |
|---------------|---------------------------------------------------------------|-----|
| <b>SsSNCA</b> | MDVFMKGLSKAKEGVVAAAEKTKQGVAEAAAGKTKEGVLYVGSKTKEGVVHGVTTVAEKT  | 60  |
| <b>HsSNCA</b> | MDVFMKGLSKAKEGVVAAAEKTKQGVAEAAAGKTKEGVLYVGSKTKEGVVHGVATVAEKT  | 60  |
| <b>BtSNCA</b> | MDVFMKGLSKAKEGVVAAAEKTKQGVAEAAAGRTKEGVLYVGSKTKEGVVHGVTTVAEKT  | 60  |
| <b>MmSNCA</b> | MDVFMKGLSKAKEGVVAAAEKTKQGVAEAAAGKTKEGVLYVGSKTKEGVVHGVTTVAETTK | 60  |
| <b>RnSNCA</b> | MDVFMKGLSKAKEGVVAAAEKTKQGVAEAAAGKTKEGVLYVGSKTKEGVVHGVTTVAEKT  | 60  |
| <b>XlSNCA</b> | MDVFMKGLSKAKEGVVAAAEKTKQGVAEAAAGKTKEGVLYVGSKTKEGVVHGVTTVAEKT  | 60  |
| <b>GgSNCA</b> | MDVFMKGLNKAKEGVVAAAEKTKQGVAEAAAGKTKEGVLYVGSRTKEGVVHGVTTVAEKT  | 60  |
|               | *****                                                         |     |
| <b>SsSNCA</b> | EQVTNVGEAVVTGVTAVAQKTVEGAGSIAAATGFGKKDQLGK-NEEGAPQEGILE---DM  | 116 |
| <b>HsSNCA</b> | EQVTNVGGAVVTGVTAVAQKTVEGAGSIAAATGFFVKDDQLGK-NEEGAPQEGILE---DM | 116 |
| <b>BtSNCA</b> | EQVTNVGEAVVTGVTAVAQKTVEGAGSIAAATGFGKKDHMGK-GEEGASQEGILE---DM  | 116 |
| <b>MmSNCA</b> | EQVTNVGGAVVTGVTAVAQKTVEGAGNIAAATGFFVKDDQMGK-GEEGYPQEGILE---DM | 116 |
| <b>RnSNCA</b> | EQVTNVGGAVVTGVTAVAQKTVEGAGNIAAATGFFVKDDQMGK-GEEGYPQEGILE---DM | 116 |
| <b>XlSNCA</b> | EQVSNVGGAVVTGVTAVAHKTVGAGNFAAATGLVKKDQ-K--NESGFGPEGTMENSEN    | 117 |
| <b>GgSNCA</b> | EQVSNVGGAVVTGVTAVAQKTVEGAGNIAAATGLVKKDQLAKQNEEGFLQEGMVNNT-DI  | 119 |
|               | *** **                                                        |     |
| <b>SsSNCA</b> | PVDPDNEAYEMPSEEGYQDYEPEA                                      | 140 |
| <b>HsSNCA</b> | PVDPDNEAYEMPSEEGYQDYEPEA                                      | 140 |
| <b>BtSNCA</b> | PVDPDNEAYEMPSEEGYQDYEPEA                                      | 140 |
| <b>MmSNCA</b> | PVDPGSEAYEMPSEEGYQDYEPEA                                      | 140 |
| <b>RnSNCA</b> | PVDPSSEAYEMPSEEGYQDYEPEA                                      | 140 |
| <b>XlSNCA</b> | PVNPNNETYEEMPPEEEYQDYDPEA                                     | 141 |
| <b>GgSNCA</b> | PVDPENEAYEMPPEEEYQDYEPEA                                      | 143 |
|               | ** * * *                                                      |     |

↓

Fig. 17

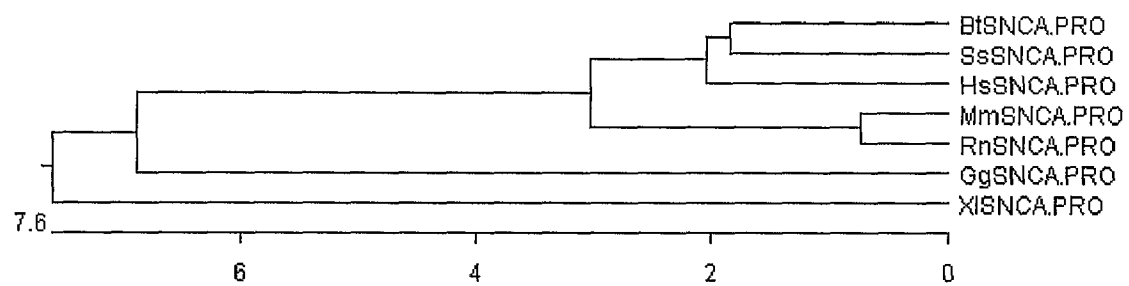


Fig. 18

1 cagtctgtta gggggaggag cttattttctc cattccgggtg tgatccagga acagctgttt  
61 tccctccagc tctgaaagtg tggggtaaag gaattcatta gccatggatg tattcatgaa  
121 aggactttca aaagccaagg agggagtcgt ggctgctgct gaaaaaacca aacagggtgt  
181 ggcagaagca ccgggaaaga caaaagaggg tgtgctctat gtaggatcca aaaccaagga  
241 aggagtgggt catggtgtga caacagtggc tgagaagacc aaagagcaag tgacaaatgt  
301 tggagaggca gtggtgacag gggtgacagc ggtagcacag aagacagtgg aaggagcagg  
361 gagcattgca gctgccactg gctttggcaa aaaggatcag ctgggcaaga atgaagaagg  
421 agccccccag gaggggaattc tggaagatat gcctgtggat cctgacaatg aagcttatga  
481 aatgccttcc gaggaagggg atcaggacta tgaaccggaa gcctaagggg tatctttgct  
541 cccagtttcc tgagatctgc tgacagacgt gccatcctgt ccaagtgcc cgttcccacc  
601 tgcccagtcg tgaccttctc tcaacgcttt cacagtgtct tttgaagtct tccatgagca  
661 gtgactggag tatctgtacc cgccccacct cggttccggg gcttccctct cactgaatat  
721 atggtagcag ggtcttgtgt gctgtggctg ttgtggcttc gaacctaaaa tgtttaatga  
781 aaaacaccta agtgactacc acttatttct aaatctattt tttgttgctg ttgagaaatt  
841 gtgagtgatt tactctccta agatttaaaa gtgtcttttc aggattccgt cgaagaataa  
901 tgatgtatgg cgaaatttgt taatatatac aatacttaaa catgtgagca tggaaactatg  
961 cacctataaa tattaactat ag

Fig. 19

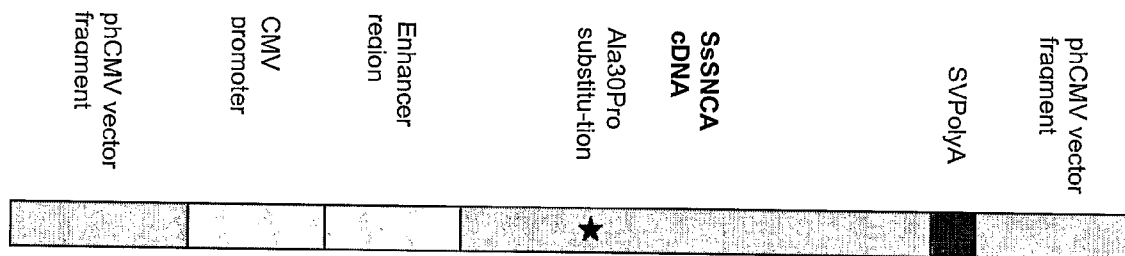


Fig. 20

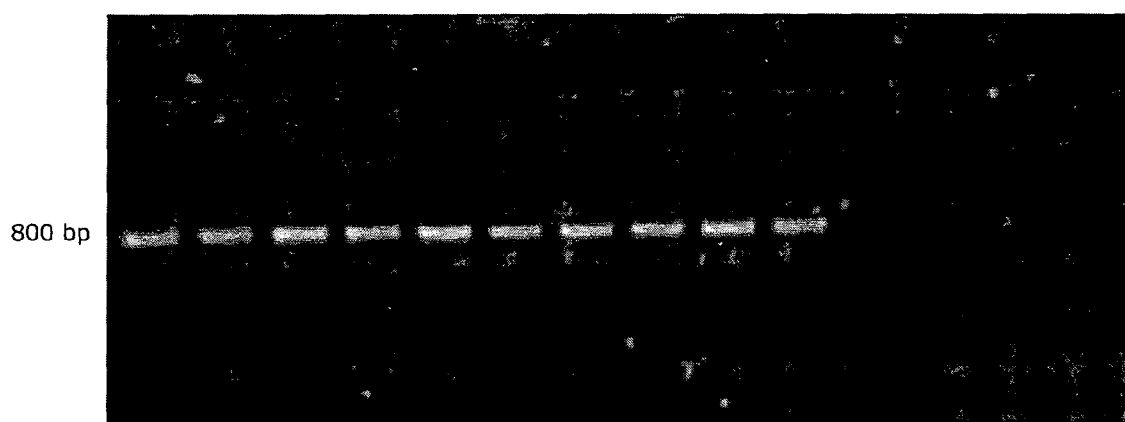


**Fig. 21**

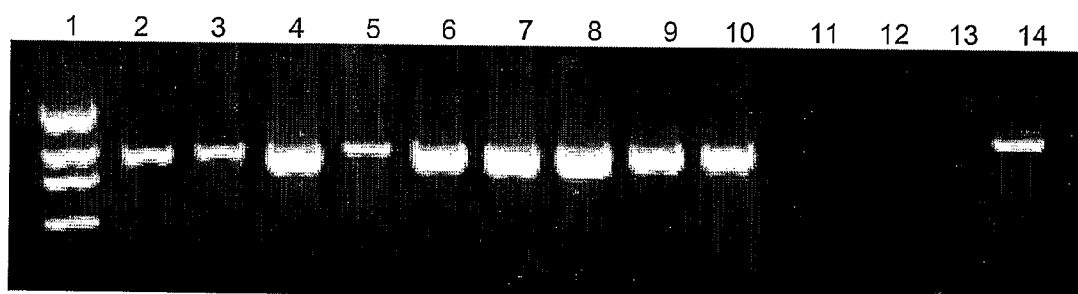


Fig. 22

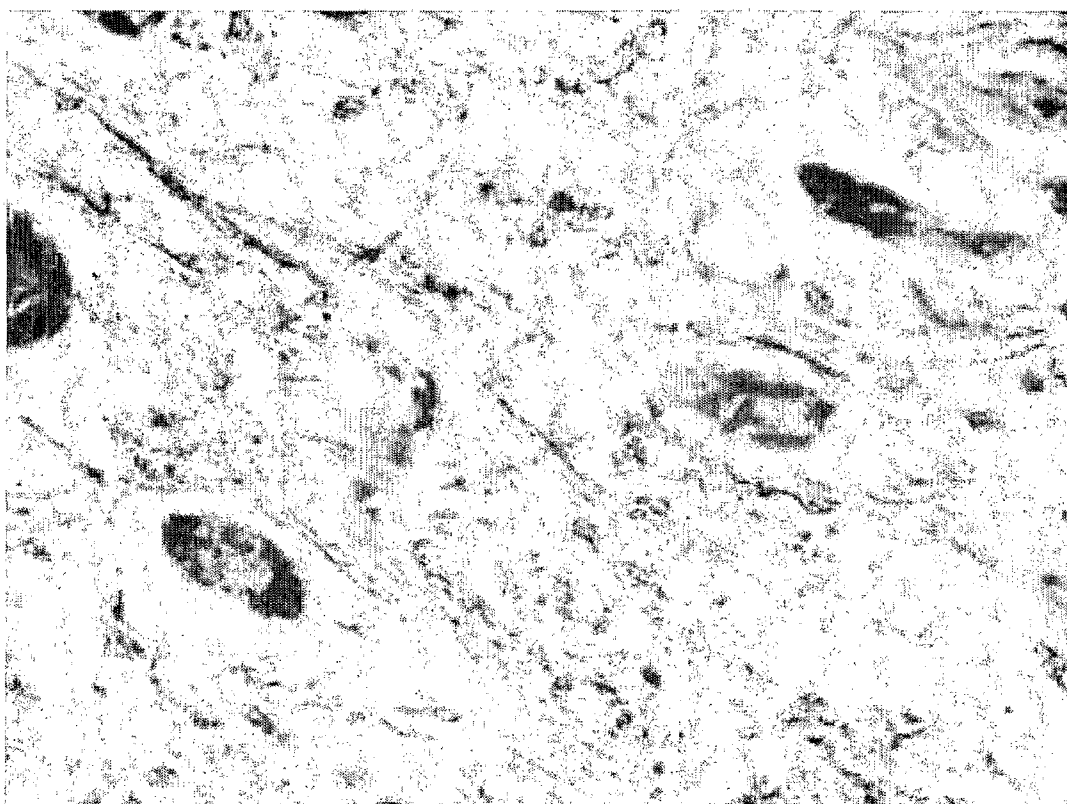


**Fig. 23**

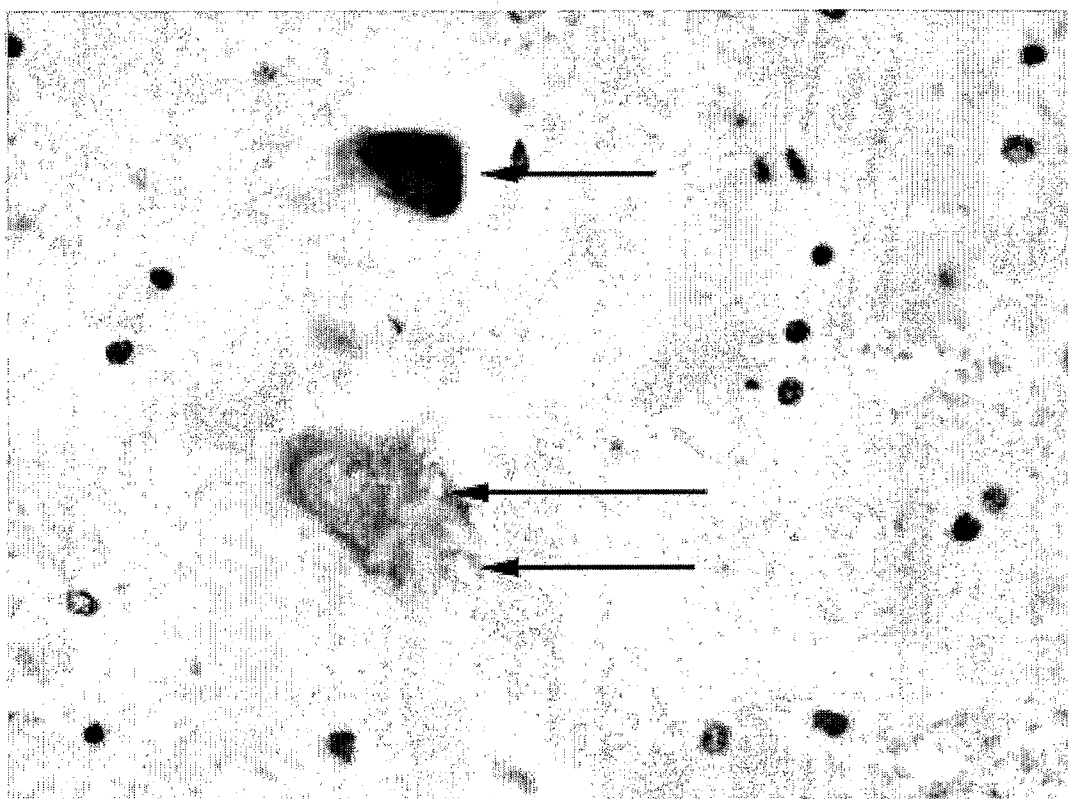
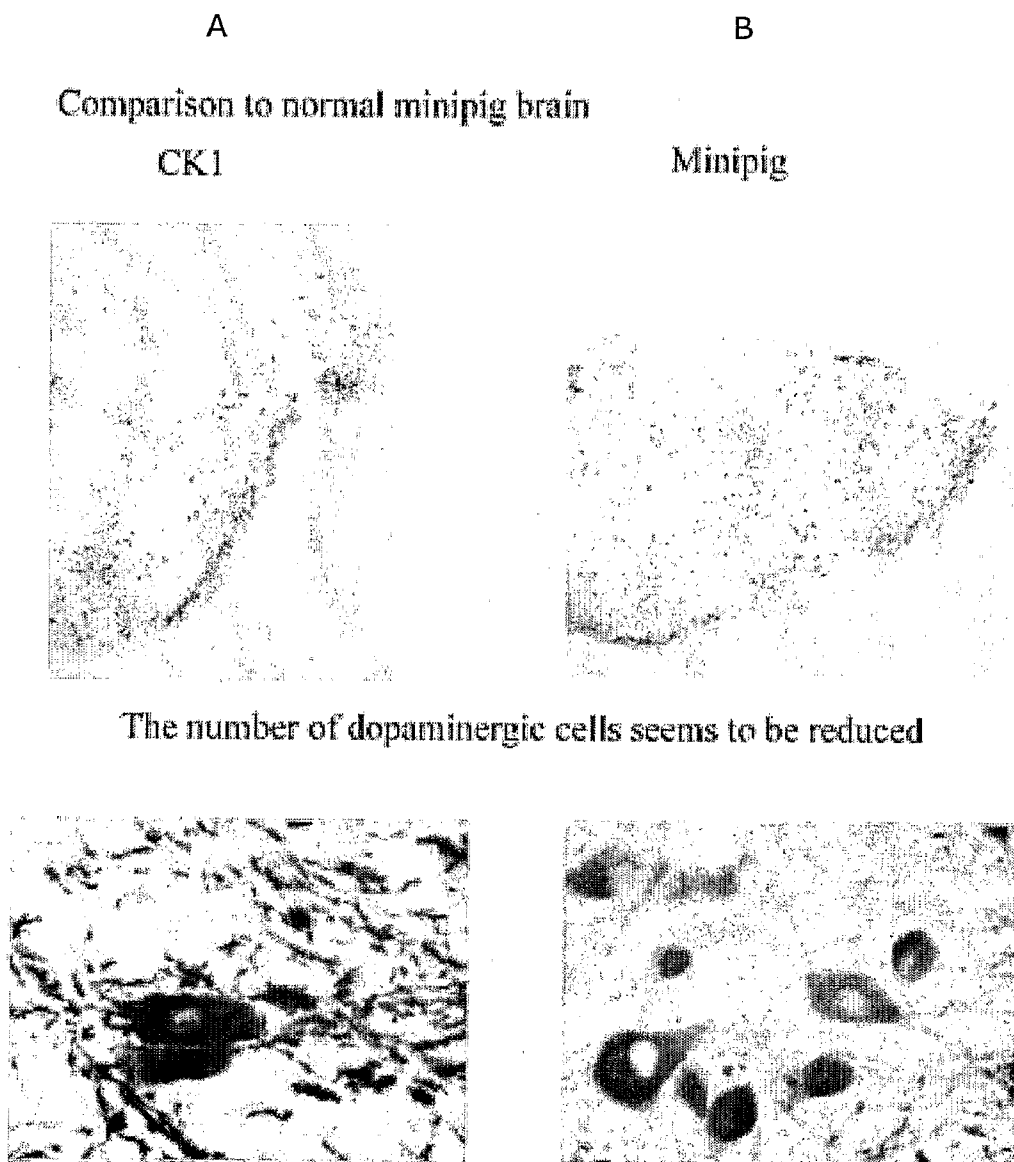


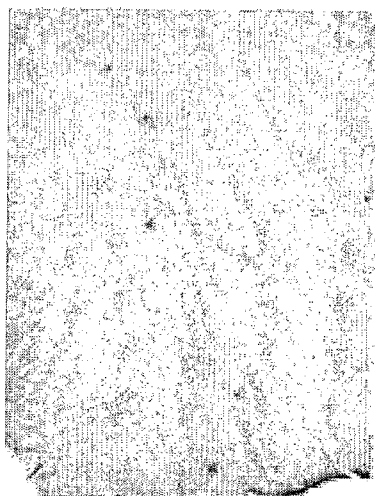
Fig. 24



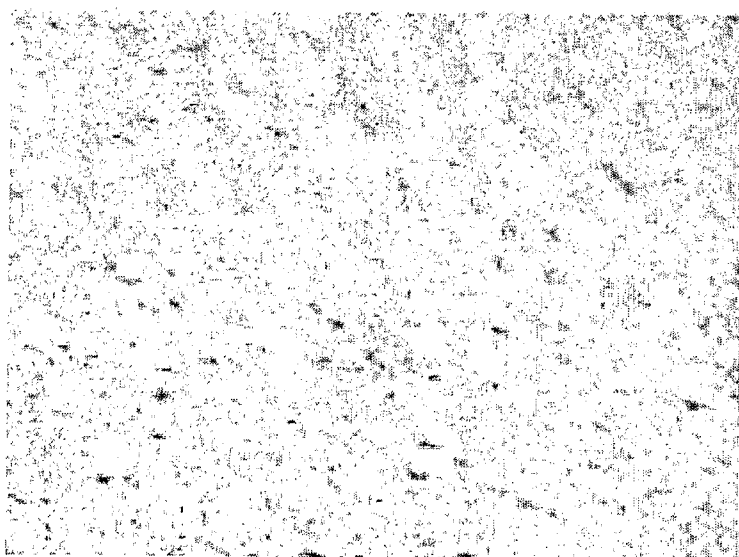
The remaining dopaminergic cells and neuropil seems to be more rough and unordered

Fig. 25

## CK1, GFAB-staining

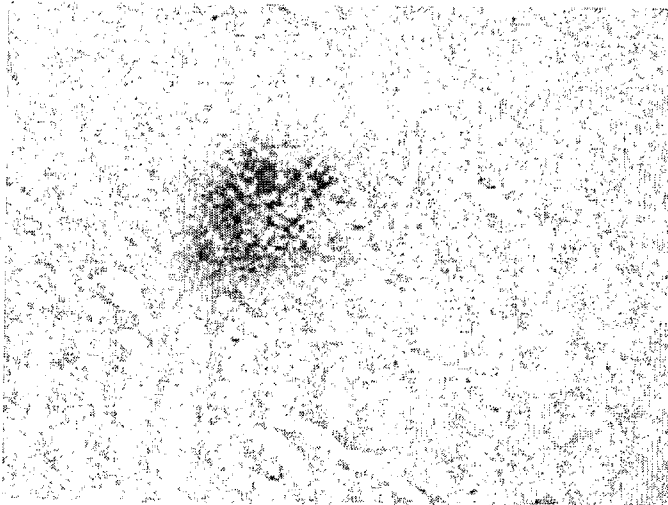


Patches of intense GFAB-staining is noted  
the mesencephalon.

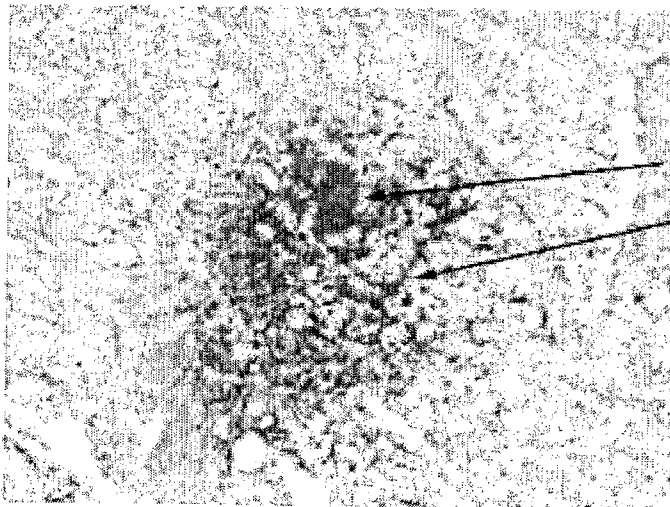


Numerous  
astrocytes is noted  
indicative  
of active  
inflammation and  
reactive gliosis.

Fig. 26



Patches of large  
alfasynuclein aggregates  
are visible throughout the  
mesencephalon



Alfasynuclein is located  
in the cell bodies and  
extracellular surroundings

**Fig. 27**

**Fig. 28**

**Fig. 29**

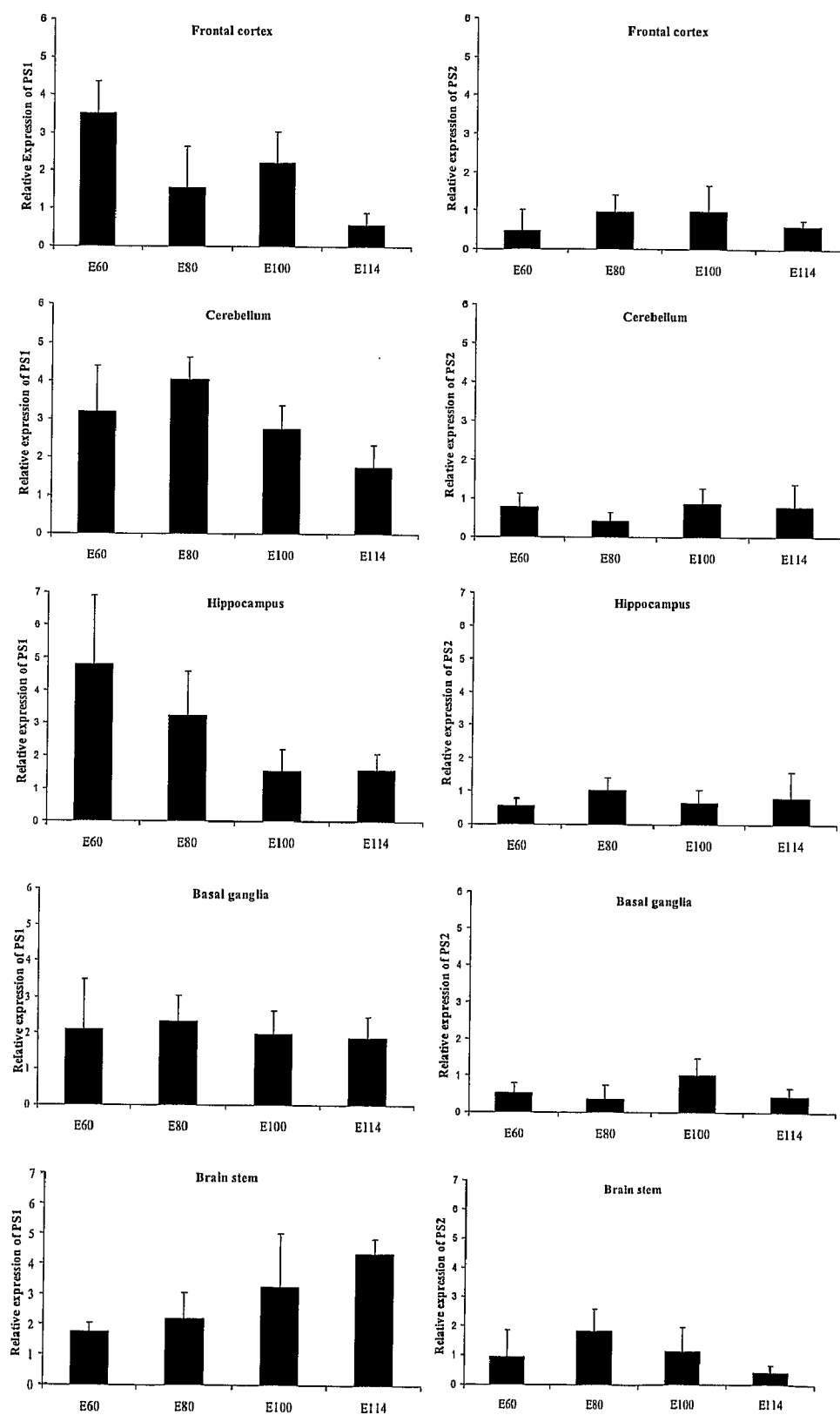


Fig. 30

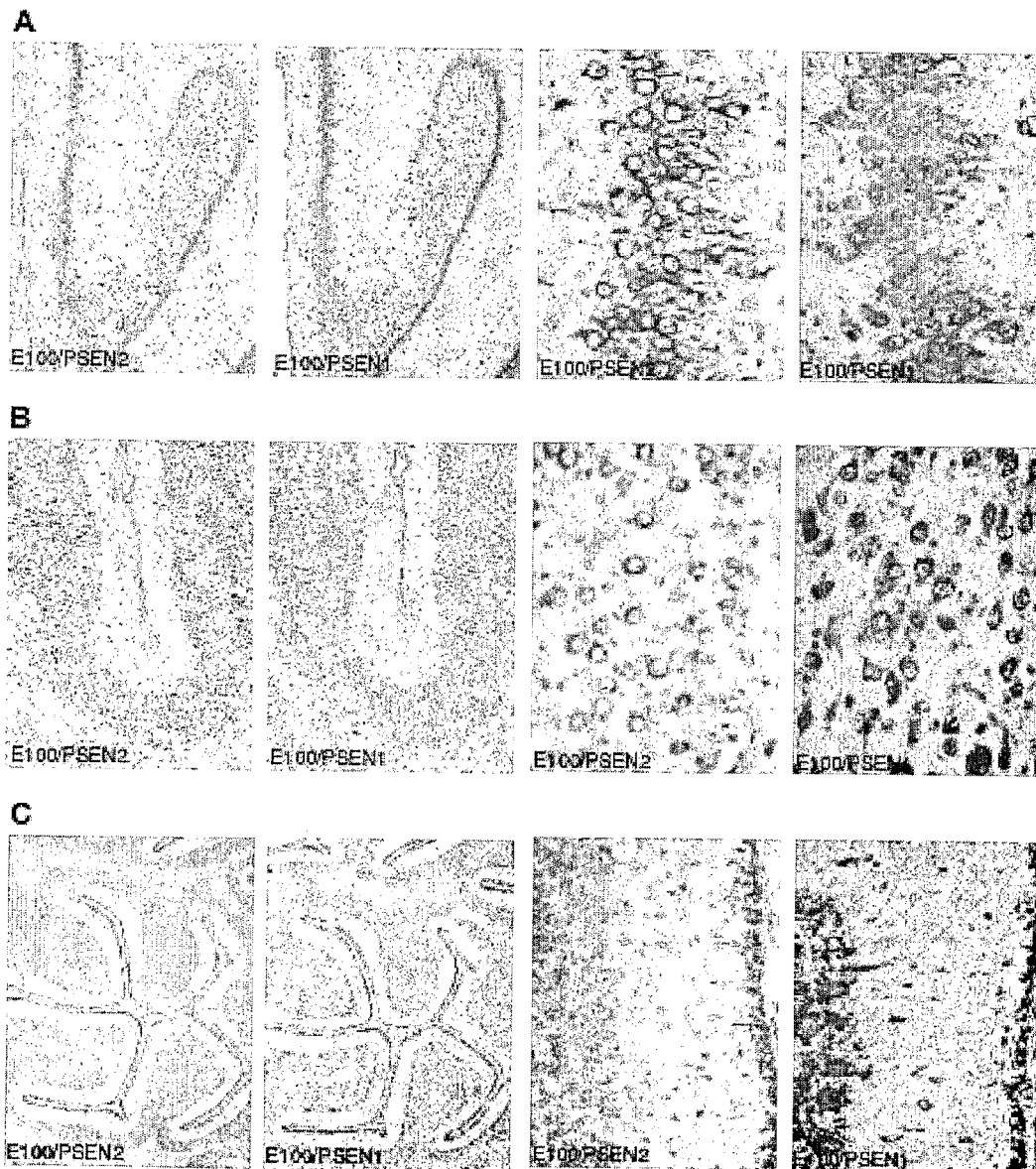


Fig. 31

**DMPK:**

|       |         |     |         |     |                       |
|-------|---------|-----|---------|-----|-----------------------|
| Pig   | (CTG) 4 |     |         |     |                       |
| Human | (CTG) n |     |         |     | normal n=5-37 / En>50 |
| Chimp | (CTG) 8 |     | GTG     |     |                       |
| Dog   | CCG     | CAG | CCG     | CTG | CCG                   |
| Rat   | (CTA) 2 | CTG | CAG     |     | CCC                   |
| Mouse |         | CTG | (CAG) 2 | CTG |                       |

**SCA12:**

|            |      |          |             |             |                            |
|------------|------|----------|-------------|-------------|----------------------------|
| Pig(Duroc) | CTG  | (CAG) n  | (CTG) 2     |             | n=8(0.7), 9(0.3)           |
| Pig(Hamp)  | CTG  | (CAG) n  | (CTG) 2     |             | n=8(0.2), 10(0.8)          |
| Pig(Land)  | CTG  | (CAG) n  | (CTG) 2     |             | n=9                        |
| Pig(York)  | CTG  | (CAG) n  | (CTG) 2     |             | n=9                        |
| Pig(Mini)  | CTG  | (CAG) n  | (CTG) 2     |             | n=9                        |
| Human      | CTG  | (CAG) n  | CTG         |             | normal n=7-28 (10) / En>65 |
| Chimp      | CTG  | (CAG) 11 | CTG         |             |                            |
| Dog        | N.P. |          |             |             |                            |
| Rat        | CTG  | (CAG) 4  |             | CAC (CAG) 3 | CTG                        |
| Mouse      | CTG  | (CAG) 2  | GAG (CAG) 2 | CAC (CAG) 3 | CTG                        |

**FMR1/FRAXA:**

|            |          |     |         |              |                                           |
|------------|----------|-----|---------|--------------|-------------------------------------------|
| Pig(Duroc) | (CGG) n  |     |         |              | n=12 (<0.1), 13(0.2), 14 (0.9), 15 (<0.1) |
| Pig(Hamp)  | (CGG) n  |     |         |              | n= 9(0.2), 13(0.1), 14(0.6), 15(0.1)      |
| Pig(Land)  | (CGG) n  |     |         |              | n=14                                      |
| Pig(York)  | (CGG) n  |     |         |              | n=13(0.1), 14(0.4), 15(0.5)               |
| Pig(Mini)  | (CGG) n  |     |         |              | n=12(0.3), 13(0.3), 14(0.4)               |
| Human      | (CGG) 14 | AGG | (CGG) n |              | normal n=6-52 / En>200                    |
| Chimp      | (CGG) 9  | AGG | CGG     | AGG (CGG) 16 | AGG CGG                                   |
| Dog        | (CGG) 12 |     |         |              |                                           |
| Rat        | (CGG) 4  | CGA | CGG     |              |                                           |
| Mouse      | (CGG) 6  | CGA | (CGG) 2 |              |                                           |

**FMR2/FRAXE:**

|       |         |         |         |         |                        |
|-------|---------|---------|---------|---------|------------------------|
| Pig   |         | (CCG) 7 | CTG     | CCG     |                        |
| Human | CCG     | GAC     | (CCG) n | CTG     | CCG                    |
| Chimp | N.P.    |         |         |         | normal n=6-35 / En>200 |
| Dog   | N.P.    |         |         |         |                        |
| Rat   | (CCG) 2 | CCA     | (CCG) 2 | CTG     | CCG                    |
| Mouse | (CCG) 4 |         |         | (CTG) 2 | CCG                    |

Fig. 32

**SCA1:**

|            |         |        |     |     |     |     |         |                                     |           |
|------------|---------|--------|-----|-----|-----|-----|---------|-------------------------------------|-----------|
| Pig(Duroc) | (CAG)n  | (CCG)4 | CCA | CCG | CCA | CCG | CAG     | n=1                                 | Q=2, P=8  |
| Pig(Hamp)  | (CAG)n  | (CCG)4 | CCA | CCG | CCA | CCG | CAG     | n=1                                 | Q=2, P=8  |
| Pig(Land)  | (CAG)n  | (CCG)4 | CCA | CCG | CCA | CCG | CAG     | n=1                                 | Q=2, P=8  |
| Pig(York)  | (CAG)n  | (CCG)4 | CCA | CCG | CCA | CCG | CAG     | n=1                                 | Q=2, P=8  |
| Pig(Mini)  | (CAG)n  | (CCG)4 | CCA | CCG | CCA | CCG | CAG     | n=1(0.2), 2(0.8)                    | Q=3, P=8  |
| Human      | (CAG)n  |        | CAT | CAG | CAT |     | (CAG)m  | normal n+m=6-39 (15) /<br>E(n+m)>40 | Q=28, H=2 |
| Chimp      | (CAG)10 |        | CAT | CAG | CAT |     | (CAG)10 |                                     | Q=21, H=2 |
| Dog        | (CAG)6  |        |     |     |     |     |         |                                     | Q=6       |
| Opossum    | CAG     | CCG    |     |     |     |     | CAG     |                                     | Q=2, P=1  |
| Rat        |         |        | CCC | CCT | CCG |     | (CAG)2  |                                     | Q=2, P=3  |
| Mouse      |         |        | CCC | CCT | CCG |     | (CAG)2  |                                     | Q=2, P=3  |

**SCA2:**

|         |         |         |         |         |         |         |                                      |           |     |
|---------|---------|---------|---------|---------|---------|---------|--------------------------------------|-----------|-----|
| Pig     | (CAG) 2 | (CAA) 2 | (CAG) 5 |         |         |         |                                      |           | Q=9 |
| Human   | (CAG) n | CAA     | (CAG) 4 | CAA     | (CAG) m | (CCG) 2 | normal n+m=13-33<br>(15) / E(n+m)>34 | Q=21, P=2 |     |
| Chimp   | (CAG) 9 | (CAA) 6 | (CAG) 3 | CAA     | (CAG) 7 | (CCG) 2 |                                      | Q=26, P=2 |     |
| Dog     | CAG     | CAA     | (CAG) 5 | (CCG) 2 | (CAG) 2 | CCG     | CAG (CCG) 2                          | Q=10, P=5 |     |
| Opossum | N.P.    |         |         |         |         |         |                                      |           |     |
| Rat     | CAG     |         |         | CCG     | CAG     |         | CCG                                  | Q=2, P=2  |     |
| Mouse   | CAG     |         |         | CCG     | CAG     |         | CCG                                  | Q=2, P=2  |     |

**SCA3:**

|            |        |        |        |     |     |                  |                                |      |
|------------|--------|--------|--------|-----|-----|------------------|--------------------------------|------|
| Pig(Duroc) | (CAG)n | CAA    |        |     |     | n=6              | Q=7                            |      |
| Pig(Hamp)  | (CAG)n | CAA    |        |     |     | n=6              | Q=7                            |      |
| Pig(Land)  | (CAG)n | CAA    |        |     |     | n=6              | Q=7                            |      |
| Pig(York)  | (CAG)n | CAA    |        |     |     | n=5(0.2), 6(0.8) | Q=6,7                          |      |
| Pig(Mini)  | (CAG)n | CAA    |        |     |     | n=5(0.5), 6(0.5) | Q=6,7                          |      |
| Human      | (CAG)2 | CAA    | AAG    | CAG | CAA | (CAG)n           | normal n=12-36 (15) /<br>En>54 | Q=14 |
| Chimp      | (CAG)5 | CAA    | AAG    | CAG | CAA | (CAG)11          |                                | Q=19 |
| Dog        | (CAG)2 | (CAA)2 | (CAG)6 | CAA | CAG |                  |                                | Q=12 |
| Opossum    | N.F.   |        |        |     |     |                  |                                |      |
| Rat        | CAA    | CAG    | CAT    | CAG | CAA | CAG              | GAA                            | Q=6  |
| Mouse      | CAA    | (CAG)5 |        |     |     |                  | GAG                            | Q=6  |

**SCA6:**

|            |         |        |                 |                            |          |
|------------|---------|--------|-----------------|----------------------------|----------|
| Pig(Duroc) | (CAG)n  | CAA    | (CAG)4          | n=5                        | Q=10     |
| Pig(Hamp)  | (CAG)n  | CAA    | (CAG)4          | n=5                        | Q=10     |
| Pig(Land)  | (CAG)n  | CAA    | (CAG)4          | n=5                        | Q=10     |
| Pig(York)  | (CAG)n  | CAA    | (CAG)4          | n=5                        | Q=10     |
| Pig(Mini)  | (CAG)n  | CAA    | (CAG)4          | n=7(0.5), 9(0.5)           | Q=12,14  |
| Human      | (CAG)n  |        |                 | normal n=4-18 (13) / En>20 | Q=13     |
| Chimp      | (CAG)11 |        |                 |                            | Q=11     |
| Dog        | (CAG)10 |        |                 |                            | Q=10     |
| Opossum    | CAG     | (CCG)2 | CAG CCG CCA CAG |                            | Q=3, P=4 |
| Rat        | N.P.    |        |                 |                            |          |
| Mouse      | N.P.    |        |                 |                            |          |

**SCA7:**

|         |         |         |         |         |                            |          |
|---------|---------|---------|---------|---------|----------------------------|----------|
| Pig     | (CAG) 5 |         |         |         |                            | Q=5      |
| Human   | (CAG) n |         |         |         | normal n=7-35 (10) / En>37 | Q=10     |
| Chimp   | (CAG) 8 |         |         |         |                            | Q=8      |
| Dog     | (CAG) 8 |         |         |         |                            | Q=8      |
| Opposum | (CAG) 2 | CAC CAG | CAC CAG | (CAC) 2 | (CAG) 4                    | Q=8, H=4 |
| Rat     | (CAG) 4 |         |         |         |                            | Q=4      |
| Mouse   | (CAG) 5 |         |         |         |                            | Q=5      |

**Fig. 33**

**DRPLA:**

|            |         |      |         |     |          |     |     |         |                               |           |
|------------|---------|------|---------|-----|----------|-----|-----|---------|-------------------------------|-----------|
| Pig(Duroc) | CAG     | CAA  | (CAG)n  | CAA | CAG      | CAA | CAG | (CAA) 2 | n=6                           | Q=14      |
| Pig(Hamp)  | CAG     | CAA  | (CAG)n  | CAA | CAG      | CAA | CAG | (CAA) 2 | n=6                           | Q=14      |
| Pig(Land)  | CAG     | CAA  | (CAG)n  | CAA | CAG      | CAA | CAG | (CAA) 2 | n=6                           | Q=14      |
| Pig(York)  | CAG     | CAA  | (CAG)n  | CAA | CAG      | CAA | CAG | (CAA) 2 | n=6                           | Q=14      |
| Pig(Mini)  | CAG     | CAA  | (CAG)n  | CAA | CAG      | CAA | CAG | (CAA) 2 | n=6(0.7), 7(0.3)              | Q=14,15   |
| Human      | CAG     | CAA  | CAG     | CAA | (CAG)n   |     |     |         | normal n=3-25<br>(13) / En>49 | Q=17      |
| Chimp      | CAG     | CAA  | CAG     | CAA | (CAG) 12 |     |     |         |                               | Q=16      |
| Dog        |         |      | (CAG) 8 | CAA | CAG      | CAA | CAG |         |                               | Q=12      |
| Opossum    | (CAG) 6 | CAA  | CAG     |     |          |     |     |         |                               | Q=8       |
| Rat        | (CAG) 5 | (CCA | CAG) 4  | CCG |          |     |     | (CAA) 2 |                               | Q=11, P=5 |
| Mouse      | (CAG) 3 | CCA  | CAG     |     |          |     |     | (CAA) 2 |                               | Q=6, P=1  |

**SCA17:**

|         |         |         |          |         |         |         |          |         |     |                         |
|---------|---------|---------|----------|---------|---------|---------|----------|---------|-----|-------------------------|
| Pig     |         |         | (CAG) 4  | CAA     | (CAG) 6 | CAA     | (CAG) 10 | CAA     |     | Q=26                    |
| Human   | (CAG) 3 | (CAA) 3 | (CAG) 8  | CAA     | CAG     | CAA     | (CAG)n   | CAA     | CAG | n=9-22<br>(18)<br>En>26 |
| Chimp   | (CAG) 3 | (CAA) 3 | (CAG) 25 | CAA     | CAG     |         |          |         |     | Q=30                    |
| Dog     | CAA     | (CAG) 6 | GCC      | (CAG) 4 | GCC     | (CAG) 5 | CAA      | (CAG) 2 | GCC | Q=22                    |
| Opossum | (CAG) 8 | CAA     | (CAG) 2  | CAA     |         |         |          |         |     | Q=12                    |
| Rat     | (CAG) 8 | CAA     | (CAG) 3  | CAA     | (CAG) 2 |         |          |         |     | Q=14                    |
| Mouse   | (CAG) 3 | CAA     | CAG      | CAA     | (CAG) 3 | (CAA) 2 | (CAG) 2  |         |     | Q=13                    |

**SBMA:**

|         |          |     |         |  |  |  |  |  |  |      |
|---------|----------|-----|---------|--|--|--|--|--|--|------|
| Pig     | (CAG) 4  | CTG | (CAG) 3 |  |  |  |  |  |  | Q=7  |
| Human   | (CAG)n   | CAA |         |  |  |  |  |  |  | Q=23 |
| Chimp   | (CAG) 21 | CAA |         |  |  |  |  |  |  | Q=22 |
| Dog     | (CAG) 10 |     |         |  |  |  |  |  |  | Q=10 |
| Opossum | (CAG)    | CAC | (CAG) 7 |  |  |  |  |  |  | Q=8  |
| Rat     | (CAG) 2  | CGG | CAG     |  |  |  |  |  |  | Q=3  |
| Mouse   | (CAG) 2  | AGG | CAG     |  |  |  |  |  |  | Q=3  |

**Huntingtin:**

|            |          |     |         |         |                    |                          |
|------------|----------|-----|---------|---------|--------------------|--------------------------|
| Pig(Duroc) | (CAG)n   |     | CAA     | (CAG) 2 | n=14(0.6), 21(0.2) | Q=17, 24                 |
|            | (CAG) 5  | CAA | (CAG) 8 | CAA     | (CAG) 2            | Q=17                     |
| Pig(Hamp)  | (CAG)n   |     | CAA     | (CAG) 2 | N=14(0.7), 15(0.3) | Q=17, 18                 |
| Pig(Land)  | (CAG) 14 |     | CAA     | (CAG) 2 | (0.8)              | Q=17                     |
|            | (CAG) 5  | CAA | (CAG) 9 | CAA     | (CAG) 2            | Q=18                     |
| Pig(York)  | (CAG) 14 |     | CAA     | (CAG) 2 | (0.5)              | Q=17                     |
|            | (CAG) 5  | CAA | (CAG)n  | CAA     | (CAG) 2            | n=4(0.2), 7(0.1), 8(0.2) |
| Pig(Mini)  | (CAG) 14 |     | CAA     | (CAG) 2 | (0.2)              | Q=17                     |
|            | (CAG) 5  | CAA | (CAG)n  | CAA     | (CAG) 2            | n=8(0.2), 9(0.6)         |
| Human      | (CAG)n   | CAA | CAG     |         |                    | Q=20                     |
| Chimp      | (CAG) 13 | CAA | CAG     |         |                    | Q=15                     |
| Dog        | (CAG) 4  | CAA | (CAG) 5 |         |                    | Q=10                     |
| Opossum    | (CAG) 6  |     |         |         |                    | Q=6                      |
| Rat        | (CAG) 2  | CAA | (CAG) 5 |         |                    | Q=8                      |
| Mouse      | (CAG) 2  | CAA | (CAG) 4 |         |                    | Q=7                      |

Fig. 33 continued/

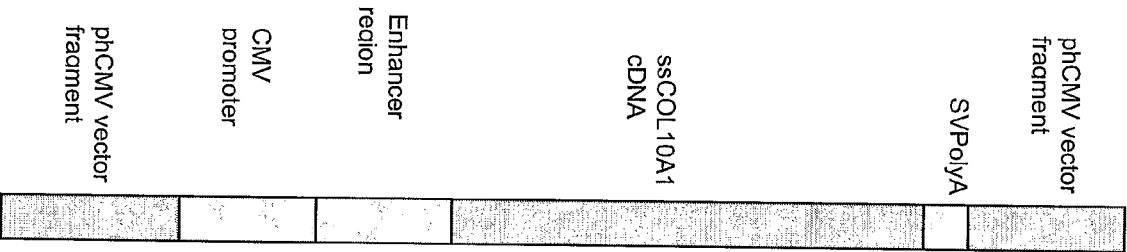


Fig. 34

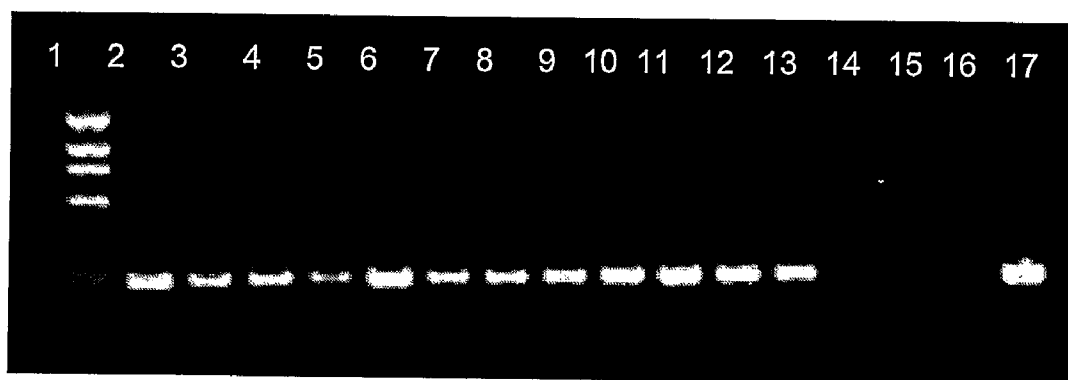


Fig. 35



Fig. 36



Fig. 37

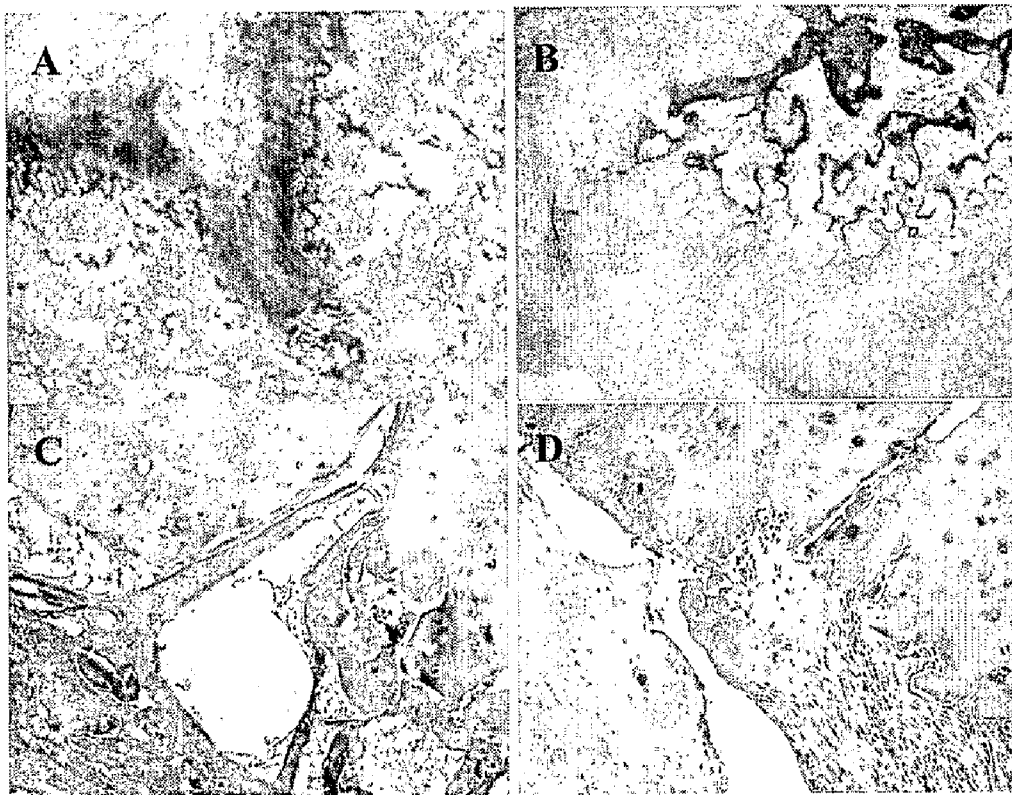


Fig. 38

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## TRANSGENIC PIG MODEL FOR A HEREDITARY NEURODEGENERATIVE AUTOSOMAL DOMINANT DISEASE

This application is a §371 national phase filing of PCT/DK2007/000204, filed Apr. 30, 2007, and claims priority to Danish Application No. PA 2006 00616, filed May 1, 2006, U.S. Provisional Application No. 60/796,196, filed May 1, 2006, and Danish Application No. PA 2007 00429, filed Mar. 20, 2007.

All patent and non-patent references cited in the application are hereby incorporated by reference in their entirety.

### FIELD OF INVENTION

The present invention relates to a non-human animal model, such as a porcine animal model, and methods for producing a non-human animal model by sperm-mediated gene transfer (SMGT). When a genetic determinant involved in a hereditary disease is used for SMGT, i.e. a genetic determinant which confers a dominant phenotype for said hereditary disease, the non-human animal model can be used for studying such hereditary diseases, such as autosomal dominant hereditary diseases, for example protein conformation diseases, such as Amyotrophic Lateral Sclerosis (ALS), Alzheimer's disease, Parkinson's disease, diseases related to trinucleotide repeats, Huntington's disease but also dyschondroplasia.

### BACKGROUND OF INVENTION

Transgenic, non-human animals can be used to understand the action of a single gene in the context of the whole animal and the interrelated phenomena of gene activation, expression, and interaction. The technology has also led to the production of models for various diseases in humans and other animals which contributes significantly to an increased understanding of genetic mechanisms and of genes associated with specific diseases.

While smaller animals, such as mice, have proved to be suitable models for certain diseases, their value as animal models for many human diseases is quite limited. Larger transgenic animals are much more suitable than mice for the study of many of the effects and treatments of most human diseases because of their greater similarity to humans in many aspects.

For the past two decades, pigs have been used in biomedical research with increasing frequency as replacements for dog and primates. This is due to the anatomical and physiological similarity to humans. Pigs and human share anatomical and physiological characteristics such as heart size, cardiac output, and coronary blood supply which have made pigs widely used in cardiac surgery, pacemaker studies and heart transplantations. Similarly, pig and humans share features in digestive physiology and pigs are therefore widely used in nutritional studies and subjects in relations to this including lipid metabolism, gastric ulceration, diabetes and alcoholism. Furthermore, porcine models are used for the study of disorders of the skin. Organs of porcine origin are also used in organ transplantation research. However, the pig constitutes an evolutionary clade in relation to humans and rodents.

Many human diseases are hereditary. The inheritance of genetic disorders, abnormalities, or traits is a function of both the type of chromosome on which the abnormal gene resides (autosomal or sex chromosome), and of the trait itself, i.e. whether the trait is dominant or recessive. The trait can be due to a single defective gene from one parent (dominant inher-

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itance) or the trait can arise when two copies of the gene (one from each parent) are defective (recessive inheritance).

Dominant inheritance occurs when an abnormal gene from one parent is capable of causing disease even though the matching gene from the other parent is normal. Accordingly, the abnormal gene dominates the outcome of the gene pair and one copy of the mutant gene is sufficient for expression of the abnormal phenotype.

Several distinct characteristics of autosomal dominant inheritance include: Every affected individual has an affected parent (except in cases of new mutations or incomplete penetrance); males and females are equally likely to inherit the allele and be affected (as the genes are located on autosomes, of which each male and female has two copies); and recurrence risk (the probability that a genetic disorder that is present in a patient will recur in another member of the family) for each child of an affected parent is  $\frac{1}{2}$  (as only one copy of a gene is necessary for development of the disease). If one parent is a heterozygote for a particular gene, their offspring will either inherit the gene or they will not, with each outcome equally likely. Accordingly, if an affected individual's siblings are not affected, they do not carry the mutation and cannot therefore pass it on to their own offspring.

As many of these autosomal dominant diseases are deleterious, one would expect that over time they would disappear from the population due to natural selection. However, there are several phenomena, cf. below, that can lead to maintenance of these alleles in the population.

Variable expressivity: the variable severity of a genetic trait. Different individuals with the same mutation will develop different degrees of the disorder due to difference in environment and the modifying effects of other genes. Because of this, a mutation that leads to a relatively mild form of the disease in one individual stands a good chance of being passed on and maintained in the population. The same mutation in another individual may lead to such a severe manifestation that the affected individual is unable to propagate the mutation to the next generation. This demonstrates very well the fact that genetic disease results as combination of genetic and environmental influences.

Late onset: when a disease has an onset later in life, affected individuals may have passed the gene to their offspring before they even knew they carried it themselves. One example of this is Huntington's disease, a late onset neurodegenerative disorder. It is now possible to receive genetic testing for this disorder, a practice that leads to many complex issues for the family undergoing the testing.

High recurrent mutation rate: 85% of cases of achondroplasia, a major cause of dwarfism, are the result of new mutations. Some segments of the genome are subject to higher than normal rates of mutation, which can lead to the maintenance of the disease in the population even if both parents were normal. This is particularly true of diseases that affect fertility. If the disease is invariably lethal at a young age, before reproduction is possible, the only source of the disease would be new mutations.

Incomplete penetrance: phenomena where a portion of individuals with a disease-associated genotype do not develop a disease. If only 30 people out of 50 who have a disease-associated mutation actually develop the disease, it is incompletely penetrant. A disease that is 75% penetrant is one in which 75% of those who carry the disease-associated mutation eventually develop the disease. The rest do not.

Transgenic animals carrying a dominant disease gene which is expressed in the animal makes it possible to study the phenotype associated with said dominant disease gene if the gene when expressed in the animal actually leads to the same

disease as in humans. Transgenic animals have traditionally been used for the improvement of livestock, and for the large scale production of biologically active pharmaceuticals. Historically, transgenic animals have been produced almost exclusively by microinjection of the fertilized egg. The pronuclei of fertilized eggs are microinjected in vitro with foreign, i.e., xenogeneic or allogeneic DNA or hybrid DNA molecules. The microinjected fertilized eggs can then be transferred to the genital tract of a pseudopregnant female.

Only a few examples of success with sperm-mediated gene transfer methods in monkeys and mice have been reported (reviewed e.g. by Vodicka (2005): *Ann. N.Y. Acad. Sci.*; 1049: 161-171; Chan (2004): *Reprod. Biol. Endocrinol.*; 2:39; and by Wall (2002): *Theriogenology*; 57: 189-201).

As noted by Wall (*ibid*), only few studies convincingly demonstrate transgene expression. Wall (*ibid*) concludes that the body of evidence is still not sufficient to warrant elevating sperm-mediated gene transfer to the status of other available state of the art methods.

Smith (2004): *Int. J. Med. Sci.*; 1(2):76-91; notes that sperm-mediated gene transfer has not yet become established as a reliable form of genetic modification and that concerted attempts to utilise sperm-mediated gene transfer often have produced negative results.

WO 2005/038001 is directed to a method for producing transgenic animals.

US 2005/0053910 pertains to cell culture media for sperm-mediated gene transfer methods.

JP 2000-316420 is related to transgene pigs obtained by methods involving micro-injection and not sperm-mediated gene transfer. The pig may carry a gene causing an autosomal, dominant disease.

However, as pigs constitute a distinct evolutionary clade in comparison with humans the introduction of mutations known as disease causing mutations in specific genes in humans cannot be expected to yield a desired phenotype in the pig model.

There is a need for improved animal models for human diseases in order to gain more information of the onset, progression and treatment regimes of hereditary diseases in humans.

### SUMMARY OF INVENTION

Until now it has been believed that the phenotypic display of an autosomal dominant disease is caused by the continuous expression of an inherited mutated gene. However, the present invention discloses that a phenotype of an autosomal dominant disease is caused by a sufficiently high expression of the mutated gene in a transient manner. Thus, the present invention discloses that the expression of a gene involved in the development of autosomal dominant diseases primarily has to be expressed in sufficiently high amounts at a specific time point during the development of the embryo of a non-human animal model. The fact that the expression of particular genes associated with autosomal dominant genes is transient also allows for the production of non-human animal models by the addition of gene products to for example embryos or other target cells (seeding effect).

In a first aspect the present invention relates to non-human animal model for a hereditary autosomal dominant disease, wherein the non-human animal model expresses at least one phenotype associated with said hereditary autosomal dominant disease obtained by a genetic determinant.

In a second aspect a non-human animal model for a hereditary autosomal dominant disease, wherein the non-human animal model expresses at least one phenotype associated

with said hereditary autosomal dominant disease obtained by sperm-mediated gene transfer.

A third aspect of the present invention pertains to a pig model for a hereditary autosomal dominant disease obtained by a genetic determinant, wherein the pig model expresses at least one phenotype associated with said hereditary autosomal disease.

A fourth aspect relates to a pig model for a hereditary autosomal dominant disease obtained by a genetic determinant, wherein said disease is a protein conformation disease.

A fifth aspect concerns a pig model for a hereditary neurodegenerative autosomal dominant disease obtained by a genetic determinant.

In further aspects of the invention is disclosed a pig model for amyotrophic lateral sclerosis, Alzheimer's Disease, Parkinson's Disease, diseases related to Trinucleotide Repeats, Huntington's chorea or dyschondroplasia obtained by a genetic determinant, wherein the pig model expresses at least one phenotype associated with Amyotrophic Lateral Sclerosis, Alzheimer's Disease, Parkinson's Disease, diseases related to Trinucleotide Repeats, Huntington's chorea or dyschondroplasia, respectively.

The present invention also relates to a method for producing the model according to the present invention, said method comprising the steps of

i) providing semen from a male, non-human animal, ii) providing at least one genetic determinant capable of establishing said at least one phenotype associated with said hereditary disease when the at least one genetic determinant is expressed in said non-human animal model, iii) contacting said semen and said at least one genetic determinant, iv) fertilising an oocyte from a female, non-human animal with the semen and the genetic material, and v) incubating said fertilised oocyte under conditions allowing said fertilised oocyte to develop into said non-human animal model.

Furthermore, a method for evaluating the response of a therapeutical treatment of a hereditary disease, said method comprising the steps of a. providing the non-human animal model according to the present invention, b. treating said non-human animal with at least one pharmaceutical composition exerting an effect on said at least one phenotype, and c. evaluating the effect observed, is disclosed.

Yet other aspects concern a non-human sperm cell comprising at least one genetic determinant exerting at least one dominant phenotype for at least one hereditary disease when expressed in a non-human animal host organism, and a method for producing the non-human sperm cell, said method comprising the steps of a. providing a non-human sperm cell, b. providing at least one genetic determinant exerting a dominant phenotype for a hereditary disease when expressed in a non-human animal host organism, c. contacting said non-human sperm cell and said at least one genetic determinant, wherein said contacting results in the uptake of the genetic determinant into the non-human sperm cell.

Moreover, the present invention also relates to a composition comprising a non-human sperm cell in combination with at least one genetic determinant exerting at least one dominant phenotype for at least one hereditary disease when expressed in a non-human animal host organism.

In further aspects the invention pertains to a method for fertilising an oocyte by sperm-mediated gene transfer, said method comprising the steps of providing the non-human sperm cell or the composition as defined above and introducing said non-human sperm cell into the oocyte to be fertilised.

The present invention also relates to an embryo obtained by fertilising an oocyte with the non-human sperm cell or with the composition as defined herein.

Yet a further aspect relates to a method for the cultivation and development of the embryo as described herein, said method comprising the step of cultivating said embryo under conditions allowing the embryo to develop into a non-human animal offspring expressing said genetic determinant and exerting a dominant phenotype for a hereditary disease.

In a final aspect is disclosed a method for screening the efficacy of a pharmaceutical composition, said method comprising the steps of a. providing the non-human animal model of the present invention, b. expressing in said animal model said at least one genetic determinant and exerting said dominant phenotype for said hereditary disease, c. administering to said non-human animal the pharmaceutical composition the efficacy of which is to be evaluated, and d. evaluating the effect, if any, of the pharmaceutical composition on the phenotype exerted by the genetic determinant when expressed in the non-human model.

#### DESCRIPTION OF FIGURES

FIG. 1: Sequence of porcine SOD1 cDNA.

FIG. 2: Sequence of the mutated porcine SOD1 cDNA.

FIG. 3: Comparison of the deduced amino acid sequence of porcine SOD1 (*S. scrofa*), with human (*H. sapiens*), mouse (*M. musculus*) and rat (*R. norvegicus*). Asterisks indicate amino acid residues that are conserved among the sequences. Dots indicate that the residues are non-conservative among the sequences, and semicolons indicate residues which are conservative. Dashes indicate gaps that have been introduced to optimize the alignment. The amino acid (G) which has shifted is marked in bold.

FIG. 4: Projection of mutations in SOD1 onto the crystal structure of the human SOD1 dimer. The Protein is shown in cartoon mode where helices are red, strands are yellow, and loops are blue. Grey areas represent regions which have been mutated in humans with ALS. The mutations are distributed all over the protein, illustrating that the majority or all of the residues in the protein are important for correct function of the enzyme.

FIG. 5: SOD1 linearised construct used to create transgenic pigs by means of SMGT. The fragment constitutes approximately 2100 bp and includes a CMV promoter, an enhancer region, the porcine SOD1 cDNA, and the SVPolyA (simian virus 40 poly A) fragment. Furthermore, the 5'- and 3'-prime end of the DNA fragment include additional bases derived from the pHCMV vector to protect crucial element from being truncated following SMGT.

FIG. 6: PCR evaluation of transgenic offspring. Lane 1: PUC 19 marker, lane 2: piglet 4905, lane 3: piglet 4906, lane 4: piglet 4907, lane 5: piglet 4908, lane 6: piglet 4909, lane 7: piglet 4910, lane 8: piglet 4911, lane 9: minus DNA, lane 10: minus DNA, lane 11: negative control, and lane 12: positive control. All the tested piglets (animal 4905-4911) from the litter are positive regarding the transgenic fragment.

FIG. 7: PCR evaluation of DNA from different tissues from animal 4906. Lane 1: PUC 19 marker, lane 2: empty, lane 3: liver, lane 4: lung, lane 5: kidney, lane 6: heart, left ventricle, lane 7: jaw muscle, lane 8: top round, lane 9: shoulder muscle, lane 10: diaphragms, lane 11: cerebellum, lane 12: hippocampus, lane 13: frontal cortex, lane 14: cervical medulla spinalis from 4909, lane 15: minus DNA, lane 16 minus DNA, lane 17 negative control, lane 18: positive control.

FIG. 8: PCR evaluation of DNA from different tissues from animal 4909. Lane 1: PUC 19 marker, lane 2: left shoulder muscle, lane 3: right Spinacea oleracea, lane 4: musculus gluteus, lane 5: musculus pectoralis major, lane 6: facial muscle, lane 7: diaphragms, lane 8: heart, left ventricle, lane

9: lung, upper right part, lane 10 kidney, lane 11: liver, lane 12: hippocampus, lane 13: frontal cortex, lane 14: minus DNA, lane 15: minus DNA, lane 16: negative control, and lane 17: positive control.

FIG. 9: PCR evaluation of DNA purified from sperm cells from boar 4905 and 4908. The DNA is purified both by means of a standard purification procedure and the miniprep purification procedure. Lane 1: marker, lane 2: 4905, standard purification procedure, lane 3: 4905, standard purification procedure, lane 4: 4905, miniprep purification procedure, lane 5: 4905, miniprep purification procedure, lane 6: 4908, standard purification procedure, lane 7: 4908, standard purification procedure, lane 8: 4908, miniprep purification procedure, lane 9: 4908, miniprep purification procedure, lane 10: minus DNA, lane 11: minus DNA, lane 12: negative control, lane 13: empty, lane 14: positive control.

FIG. 10: PCR evaluation of transgenic offspring. Lane 1: DNA ladder, lane 2: pig 4905, lane 3: piglet 4908, lane 4: pig 4909, lane 5: pig 4906, lane 6: pig 4907, lane 7: pig 4911, lane 8: pig 4910, lane 9: wild type animal, lane 10: minus DNA, and lane 11: positive control.

FIG. 11: Southern blot. Lane 1-3: genomic DNA from boar 4905, 4908, and wt-pig digested with Pvu II, lane 4-6: genomic DNA from boar 4905, 4908, and wt-pig digested with Pvu II and BAM HI, lane 7-9: undigested genomic DNA from boar 4905, 4908, and wt-pig lane 10: SOD1 fragment used in SMGT digested with Pvu II (1-5 copies), lane 11: SOD1 fragment used in SMGT digested with Pvu II and Bam HI (1-5 copies).

FIG. 12: Analysis of porcine WT SOD1 expression levels in various porcine tissues by quantitative real-time RT-PCR. A) Detection of porcine endogenous SOD1, showing both SOD1 standard dilution and samples from the two affected boars and wild type controls, showing no difference. B) Detection of mutated porcine SOD1. Pink and yellow curves represent amplification of the mutated SOD1 fragment in various dilutions. Blue and green curves shows the lack of amplification of mutated SOD1 in both wild type and affected boars. C) SOD1 endogenous expression analysis. Each sample was conducted in triplicate. The expression analysis was performed on samples from heart, kidney, liver, lung, spleen, medulla spinalis (*M. spinalis*), frontal cortex (FCO), parietal cortex (PCO), musculus longissimus dorsi (*M. L. dorsi*), musculus semitendinosus, left side (*M.semit. l.*), musculus semitendinosus, right side (*M.semit. r.*), musculus semibranosus, left side (*M.semb. l.*), and musculus semibranosus, left side (*M.semb. r.*) from the two affected boars (4905 and 4908) and two wild type control boars (147 and 3713). SOD1 expression levels were normalized against the 18S ribosomal gene.

FIG. 13: SOD activity in serum from symptomatic animals (4905 and 4908) and a healthy control (4368).

FIG. 14: Investigation of muscle fibers, type 1, in affected boars (4905 and 4908) and healthy wild type controls (3713 and 147). The number of type I muscle fibers in each muscle cluster was counted in musculus longissimus dorsi, and the frequency of muscle fibers in each cluster for the four boars are shown in the histograms. The stainings represents typical type I muscle fibers from musculus longissimus dorsi from the four boars.

FIG. 15: Photomicrographs of immunohistochemistry sections from cervical spinal cord showing motoneuron from A) the affected boar (4908) and B) an unaffected wild type control (147) stained with the 100-115 anti-SOD1 peptide antibody.

FIG. 16: The porcine SNCA cDNA sequence.

FIG. 17: Alignment of the porcine  $\alpha$ -synuclein protein with  $\alpha$ -synucleins from other species. Human mutants: A30P, E46K and A53T are indicated by bold and underlined letters. Differences between the human and the porcine sequences are indicated by old blue letters. Asterisks indicate amino acid residues that are conserved among the sequences. The amino acid Ala30 substituted by a Pro in the mutated SNCA sequence is marked by an arrow.

FIG. 18: Phylogenetic tree (unrooted) of porcine alpha-synuclein, and other alpha-synuclein proteins. The tree was constructed using the using the clustal method of DNASTAR Megalign (DNASTAR Inc., Madison, Wis.) based on amino acid similarities of the full sequences. The length of each pair of branches represents the distance between sequence pairs, while the units at the bottom of the tree indicate the number of substitution events. The following abbreviations for species acronyms are used along with: Ss=*Sus scrofa*; Hs=*Homo sapiens*; Bt=*Bos taurus*; Mm=*Mus musculus*; Rn=*Rattus norvegicus*; Gg=*Gallus gallus*; Xl=*Xenopus laevis*. The Accession numbers of the sequences used for construction of the phylogenetic tree are: SsSNCA (AY049786); HsSNCA (NM\_001037145); BtSNCA (NM\_001034041); MmSNCA (AF44672); RnSNCA (NM\_019169); GgSNCA (NM\_204673); XlSNCA (BC054200).

FIG. 19: The mutated porcine SNCA cDNA sequence. The substituted nucleotide is shown as a bold underlined letter.

FIG. 20: SNCA-phCMV1 linearized construct used to create transgenic pigs by means of SMGT. The fragment constitutes approximately 2100 bp and includes a CMV promoter, an enhancer region, the mutated (A30P) porcine SNCA cDNA, and the SVPolyA (simian virus 40 poly(A) fragment. Furthermore, the 5'- and 3'-prime end of the DNA fragment include additional bases derived from the phCMV vector to protect crucial element from being truncated following SMGT.

FIG. 21: PCR evaluation of transgenic offspring. Lane 1: piglet 4363, lane 2: piglet 4364, lane 3: piglet 4365, lane 4: piglet 4366, lane 5: piglet 4367, lane 6: piglet 4368, lane 7: piglet 4369, lane 8: piglet 4370, lane 9: piglet 4371, lanes 10 and 11: positive control, lanes 12 and 13: minus DNA, lane 14: untransformed control. All the tested piglets (animal 4363-4371) from the litter are positive regarding the transgenic fragment.

FIG. 22: PCR evaluation of DNA purified from sperm cells from boars 4363-4371. The DNA is purified both by means of a standard purification procedure. Lane 1: DNA marker, lane 2: 4363, lane 3: 4364, lane 4: 4365, lane 5: 4366, lane 6: 4367, lane 7: 4368, lane 8: 4369, lane 9: 4370, lane 10: 4371, lane 11: minus DNA, lanes 12 and 13: negative control, lane 14: positive control.

FIG. 23: Nissl AMG staining of thin-layer sections from substantia nigra of boar #4363. Neurons in substantia nigra abnormal; presence of cytoplasmic vacuoles and shrinking of cells. Lewy bodies are not visible and this staining.

FIG. 24: HE staining of thin-layer sections from substantia nigra of boar #4363. Neurons are shrunken and with numerous lacunae.

FIG. 25: TH staining of thin-layer sections from substantia nigra of boar #4363 (A) and a minipig control (B). The number of dopaminergic cells are reduced in 4363. Remaining dopaminergic cells and neuropil appear more rough and unordered (lower panels).

FIG. 26: GFAB staining of thin-layer sections from substantia nigra of boar #4363. Intense GFAB staining is seen in the mesencephalon. Numerous astrocytes are present indicative of active inflammation and reactive gliosis.

FIG. 27:  $\alpha$ -synuclein Ab staining of thin-layer sections from substantia nigra of boar #4363.

FIG. 28: Multiple amino acid sequence alignment of PSEN1. The alignment was performed using Clustal W. The sequences are *Sus scrofa* (DQ853416), *Bos Taurus* (NM 174721), *Homo sapiens* (NM 000021), and *Mus musculus* (NM 008943). Asterisk (\*) indicates amino acids conserved among the sequences; Above the sequence alignments are by (+) indicated the position of pathogenic missense mutations identified in human PSEN1. Also the position of human missense SNPs are indicated above the sequence alignments with the alternative amino acids in bold.

FIG. 29: Multiple amino acid sequence alignment of PSEN2. The alignment was performed using Clustal W. The sequences are *Sus scrofa* (DQ853415), *Bos Taurus* (NM 174440), *Homo sapiens* (NM 000447), and *Mus musculus* (NM 011183). Asterisk (\*) indicates conserved amino acids among the sequences. Above the sequence alignments are by (+) indicated the position of pathogenic missense mutations identified in human PSEN2. Also the position of a human missense SNP is indicated above the sequence alignments with the alternative amino acid in bold.

FIG. 30: Analysis of porcine PSEN1 and PSEN2 expression levels in the developing pig brain by quantitative real-time RT-PCR. Quantitative results are presented as normalized mean ( $\pm$ SD). For quantification and statistical analysis see materials and methods section. Each sample was run both in three biological and three technical triplicates. The expression analysis was performed on samples from frontal cortex, cerebellum, hippocampus, basal ganglia, and brain stem derived from embryonic days 60, 80, 100, and 115 (E60, E80, E100, and E115).

FIG. 31: Immunohistochemical analysis of PSEN1 and PSEN2 expression in embryonic E100 porcine brains. Brain sections were immunohistochemical stained for PSEN1 or PSEN2 and nuclei counterstained by haematoxylin. Sections illustrating PSEN1 and PSEN2 staining patterns in hippocampus (A), cortex (B), and cerebellum (C) are shown for embryonic day E100. Higher magnitude illustrations of neurons representative for each of the three regions are shown in the right part of each panel.

FIG. 32: Sequence alignment of non-coding TNRs from human, pig, and mouse. For the human sequences the most common identified alleles are shown with the variable number of TNRs indicated. Within brackets the most common occurring number of TNRs is shown. Note that human and chimpanzee alleles are highly polymorphic and only one representative sequence is shown. For the porcine sequences the allele frequencies are shown in brackets, furthermore, the identified alleles are revealed. N.P. indicates that a corresponding genomic sequence not was extractable from NCBI. En indicates the number of repeats present minimal in disease causing human alleles.

FIG. 33: Sequence alignment of poly-glutamine encoding TNRs in pig, human, chimpanzee (chimp), dog, opossum, rat, and mouse. For the human sequences the most common alleles are shown with the variable number of TNRs indicated. The most common number of TNRs are shown in brackets. Note that human and chimpanzee alleles are highly polymorphic and only one representative sequence is shown. For the porcine sequences the different alleles are shown and the number in brackets indicates the frequency of each allele. Q indicates the number of glutamines, H the number of histidines, and P the number of prolines. For the Huntingtin gene additional alleles with potential to encode 14 or 15 poly-glutamines were identified in a larger Yorkshire and Landrace sample cohort (see table 1). N.P. indicates that a correspond-

ing genomic sequence not was extractable from NCBI. En indicates the number of repeats present minimal in disease causing human alleles.

FIG. 34: COL10A1 linearised construct used to create transgenic pigs by means of SMGT. The fragment constitutes approximately 3600 bp and includes 5' and 3' prime phCMV vector fragment, a CMV promoter, an enhancer region, the porcine SOD1 cDNA, and the SVPolyA (simian virus 40 polyA).

FIG. 35: Examples of PCR analyses. PCR was performed on genomic DNA extracted from whole blood. Lane 1; PUC19 DNA Ladder, lanes 2-13 indicate the 12 piglets born, lanes 14-15; no DNA added, lane 16; negative control (wild type pig), lane 17; positive control.

FIG. 36: Southern Blot analysis. Lane 1: Bgl II digested genomic DNA from the affected pig, lane 2: Bgl II digested genomic DNA from wt pig, lane 3: Bgl II and Bam HI digested genomic DNA from affected pig, lane 4 Bgl II and Bam HI digested genomic DNA from wt pig. Bgl II digestion. Bgl II only digested the DNA to a limited degree (lane 1 and 2), lane 3 and for show additional bands in the diseased sow, showing that the transgene is integrated into the genome.

FIG. 37: Analysis of COL10A1 expression in various porcine tissues. Lane 2-11 represents the diseased transgenic pig and lane 12-16 represent a wild type pig. Lane 1; DNA ladder, lane 2; musculus triceps brachii (left), lane 3; musculus triceps brachii (right), lane 4; ovary, lane 5; kidney, lane 6; skin, lane 7; liver, lane 8; lung, lane 9; musculus longissimus dorsi, lane 10; musculus semimembranosus (left), lane 11; heart, lane 12; liver, lane 13; spleen, lane 14; kidney, lane 15; lung, lane 16; heart, lane 17-18; -DNA, lane 19; positive control, lane 20; DNA ladder.

FIG. 38: Histopathological investigation of one of the affected forelegs. A) Distal humeral physis. An area of hypertrophic, non-ossified chondrocytes of the growth plate is retained within the metaphysic area. Safranin O, obj.x1. B) Distal humeral physis. At the margins of the growth plates non-ossified, hypertrophic chondrocytes are localized. Van Gieson, obj.x2. C) Articular-epiphysial junction from the elbow joint. Within the retained cartilage cavitations with contents of fibrin are present. HE, obj.x10. D) Articular-epiphysial junction from the elbow joint. Clefts and adjacent fibrosis is present within the chondroid tissue of the articular-epiphysial junction. HE, obj.x20.

## DETAILED DESCRIPTION OF THE INVENTION

### Definitions

For purposes of the present invention, the following terms are defined below.

The term "sperm" is used to refer to a male gamete cell and includes, without limitation, spermatogonia, primary and secondary permatocytes, spermatids, differentiating spermatids, round spermatids, and spermatozoa.

The term "oocyte" is used to refer to a female gamete cell, and includes primary oocytes, secondary oocytes, and mature, unfertilized ovum.

In some cases the term "embryo" is used to describe a fertilized oocyte after implantation in the uterus until 8 weeks after fertilization at which stage it becomes a foetus. According to this definition the fertilized oocyte is often called a pre-embryo until implantation occurs. However, throughout this patent application we will use a broader definition of the term embryo, which includes the pre-embryo phase. It thus encompasses all developmental stages from the fertilization of the oocyte through morula, blastocyst stages hatching and implantation. An embryo is approximately spherical and is

composed of one or more cells (blastomeres) surrounded by a gelatine-like shell, the acellular matrix known as the zona pellucida. The zona pellucida performs a variety of functions until the embryo hatches, and is a good landmark for embryo evaluation. An embryo is formed when an oocyte is fertilized by fusion or injection of a sperm cell (spermatozoa). The fertilised oocyte is traditionally called an embryo for the first 8 weeks. After that (i.e. after eight weeks and when all major organs have been formed) it is called a foetus. However the distinction between embryo and foetus is not generally well defined. During embryonic development, blastomere numbers increase geometrically (1-2-4-8-16-etc.). Synchronous cell division is generally maintained to the 16-cell stage in embryos. After that, cell division becomes asynchronous and finally individual cells possess their own cell cycle. At about the 32-cell stage (morula stage), embryos undergo compaction, as inter-cell adhesion occur when adhesion proteins are expressed.

Accordingly, the term embryo is used in the following to denote each of the stages fertilized oocyte, zygote, 2-cell, 4-cell, 8-cell, 16-cell, morula, blastocyst, expanded blastocyst and hatched blastocyst, as well as all stages in between (e.g. 3-cell or 5-cell).

The term "non-human animal" can be a non-human primate, e.g., an ape or a monkey; and a farm animal, such as an animal selected from the group consisting of cattle, swine; sheep; goats; horses; and donkeys. Accordingly, the non-human animal can e.g. be a cow, a bull, a bison, a buffalo, a pig, a big-horn sheep, a pony, a mule, a deer, an elk, a lama, and an alpaca. Similarly the non-human animal can be a rodent, such as a mouse or rat.

The term "non-human animal model" refers to any non-human animal in which one or more cells comprise genetic determinants. The non-human animal comprising genetic determinants may for example be the result of introduction of the genetic determinant by sperm-mediated gene transfer. However, the genetic determinant may also be introduced for example by injection into cells or tissues desired.

The term "genetic determinant" of the present invention refers to genes or parts thereof, transcriptional products or parts thereof and/or translational products or part thereof that confer the display of one or more features of phenotypes of autosomal dominant hereditary diseases. Thus, in some embodiments the term "genetic determinant" is used herein to refer to a single-stranded or double-stranded "polynucleotide molecule" or "nucleic acid" comprising a structural gene of interest. The "genetic determinant" encodes a protein not ordinarily made in appreciable amounts in the target cells.

The term genetic determinant is also used to refer to a single-stranded or double stranded ribonucleic acid, RNA expressed from a gene of interest. Thus, "genetic determinants" include nucleic acids which are not ordinarily found in the genome of the target cell. "Genetic determinants" also include nucleic acids which are ordinarily found within the genome of the target cell, but is in a form which allows for the expression of proteins which are not ordinarily expressed in the target cells in appreciable amounts. Alternatively, "genetic determinants" may encode a variant or mutant form of a naturally-occurring protein.

The term genetic determinant is also used herein to refer to a protein or part thereof or a RNA molecule or part thereof of a gene of interest, wherein the gene or polynucleotide encoding said protein or RNA is not present in the target cell. Throughout the description and claims either the three letter code or the one letter code for natural amino acids are used. Where the L or D form has not been specified it is to be understood that the amino acid in question has the natural L

form, cf. Pure & Appl. Chem. Vol. (56(5) pp 595-624 (1984) or the D form, so that the peptides formed may be constituted of amino acids of L form, D form, or a sequence of mixed L forms and D forms.

Where nothing is specified it is to be understood that the C-terminal amino acid of a peptide for use according to the invention exists as the free carboxylic acid, this may also be specified as “—OH”. However, the C-terminal amino acid of a peptide for use according to the invention may be the amidated derivative, which is indicated as “—NH<sub>2</sub>”. Where nothing else is stated the N-terminal amino acid of a polypeptide comprises a free amino-group, this may also be specified as “H-”.

A peptide, fragment, homologue or variant for use according to the invention can also comprise one or several unnatural amino acids.

Conservative amino acid substitutions: Substitutions within the groups of amino acids, shown below, are considered conservative amino acid substitutions. Substitutions between the different groups of amino acids are considered non-conservative amino acid substitutions.

P, A, G, S, T (neutral, weakly hydrophobic)

Q, N, E, D, B, Z (hydrophilic, acid amine)

H, K, R (hydrophilic, basic)

F, Y, W (hydrophobic, aromatic)

L, I, V, M (hydrophobic)

C (cross-link forming)

In one embodiment the genetic determinant is in the form of microRNAs (miRNA) that are single-stranded RNA molecules of about 21-23 nucleotides in length. miRNAs are typically encoded by genes that are transcribed from DNA but not translated into protein (non-coding RNA); instead they are processed from primary transcripts known as pri-miRNA to short stem-loop structures called pre-miRNA and finally to functional miRNA. Mature miRNA molecules are partially complementary to one or more messenger RNA. Thus, protein or RNA may be produced outside the target cell and introduced into a target cell by any method known to the skilled person. For example the genetic determinant is provided from extracts of brains from diseased subjects, such as humans or animals of the present invention. Subsequently, said brain tissue is introduced into a target cell of the present invention.

The target cell may be a sperm cell, an oocyte, a fertilized oocyte, an embryo, which includes the pre-embryo phase encompassing all developmental stages from the fertilization of the oocyte through morula, blastocyst stages hatching and implantation, a fetus, or a cell derived from tissue of the developing fetus. In one embodiment of the present invention the target cell is an adult animal or tissue thereof.

The genetic determinant may be introduced to the target cell by for example injection, virus-mediated transfer or similar methods known to the skilled person.

The genetic determinant may in the form of RNA or protein be introduced into the target cell to yield a non-human animal model for autosomal dominant diseases, such as neurodegenerative diseases as described elsewhere herein, for example protein conformation disorders. In preferred embodiments the genetic determinant is introduced into the target cell to produce a pig model expressing at least one phenotype associated with ALS, Alzheimer's disease, Parkinson's disease, Huntington's chorea, diseases related to trinucleotide repeats. Similarly, in one particular embodiment a pig model is produced expressing at least one phenotype associated with dyschondroplasia.

The genetic determinant may in particular embodiments be introduced by sperm-mediated gene transfer to produce a pig

model for autosomal dominant diseases, such as neurodegenerative diseases as described elsewhere herein, for example protein conformation disorders. In preferred embodiments the genetic determinant is introduced by sperm mediated gene transfer to produce a pig model expressing at least one phenotype associated with ALS, Alzheimer's disease, Parkinson's disease, Huntington's chorea, diseases related to trinucleotide repeats. Similarly, in one particular embodiment a pig model is produced expressing at least one phenotype associated with dyschondroplasia.

The genetic determinant when present as a gene or DNA construct need not be integrated into the genome of the target cell, fertilised oocyte, embryo, fetus or tissue. In such an example the gene or DNA construct needs to be expressed in an amount sufficient for triggering a cascade that eventually results in the onset and progression of the disease in question. This is in particular the case for autosomal diseases of the neurodegenerative kind, such as protein conformation diseases. Thus, the genetic determinant involved in ALS, Alzheimer's Disease, Parkinson's disease, diseases related to trinucleotide repeats and Huntington's chorea need not to be integrated in the genome of the pig model. The expression of the gene of interest or DNA construct need not be continuous but has to take place during the development of the embryo to fetus. Similarly, when the genetic determinant is present in the form of protein where the protein is involved in the development of protein conformation diseases the protein need to be present in the embryo or fetus but need not be present continuously in the pig model.

The genetic determinant when present in the form of DNA or cDNA may further comprise regulatory sequences to direct expression of the DNA or cDNA. Such regulatory sequences may be promoters or enhancers. The term promoter will be used here to refer to a group of transcriptional control modules that are clustered around the initiation site for RNA polymerase II. Promoters are composed of discrete functional modules, each consisting of approximately 7-20 bp of DNA, and containing one or more recognition sites for transcriptional activator proteins. At least one module in each promoter functions to position the start site for RNA synthesis. The best known example of this is the TATA box.

Additional promoter elements regulate the frequency of transcriptional initiation. Typically, these are located in the region 30-110 bp upstream of the start site, although a number of promoters have recently been shown to contain functional elements downstream of the start site as well. The spacing between elements is flexible, so that promoter function is preserved when elements are inverted or moved relative to one another. Enhancers were originally detected as genetic elements that increased transcription from a promoter located at a distant position on the same molecule of DNA. The basic distinction between enhancers and promoters is operational. An enhancer region as a whole must be able to stimulate transcription at a distance; this need not be true of a promoter region or its component elements. On the other hand, a promoter must have one or more elements that direct initiation of RNA synthesis at a particular site and in a particular orientation, whereas enhancers lack these specificities. Aside from this operational distinction, enhancers and promoters are very similar entities. They have the same general function of activating transcription in the cell. They are often overlapping and contiguous, often seeming to have a very similar modular organization.

The terms “polynucleotide” and “nucleic acid” are used interchangeably, and, when used in singular or plural, generally refers to any polyribonucleotide or polydeoxyribonucleotide, which may be unmodified RNA or DNA or modified

RNA or DNA. Thus, for instance, polynucleotides as defined herein include, without limitation, single- and double-stranded DNA, DNA including single- and double-stranded regions, single- and double-stranded RNA, and RNA including single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or include single- and double-stranded regions. In addition, the term “polynucleotide” as used herein refers to triple-stranded regions comprising RNA or DNA or both RNA and DNA. The strands in such regions may be from the same molecule or from different molecules. The regions may include all of one or more of the molecules, but more typically involve only a region of some of the molecules. One of the molecules of a triple-helical region often is an oligonucleotide. The term “polynucleotide” specifically includes cDNAs. The term includes DNAs (including cDNAs) and RNAs that contain one or more modified bases. Thus, DNAs or RNAs with backbones modified for stability or for other reasons are “polynucleotides” as that term is intended herein. Moreover, DNAs or RNAs comprising unusual bases, such as inosine, or modified bases, such as triitated bases, are included within the term “polynucleotides” as defined herein. In general, the term “polynucleotide” embraces all chemically, enzymatically and/or metabolically modified forms of unmodified polynucleotides, as well as the chemical forms of DNA and RNA characteristic of viruses and cells, including simple and complex cells.

“Sperm mediated gene transfer” as used herein refers to any method wherein a non-human animal sperm cell is mixed with a genetic determinant (gene) under conditions resulting in the genetic determinant being 1) taken up by the sperm cell, 2) occurring as extrachromosomal DNA or as stably integrated into the genetic material (genome) harboured by the sperm cell, and 3) optionally expressed in said sperm cell. Once taken up by the sperm cell, the genetic material (gene) can be transferred to a non-human animal model which allows one to study the expression of the genetic determinant in the chosen genetic background.

“Autosomal diseases” are used herein to refer to diseases which are inherited through the non-sex chromosomes (pairs 1 through 22). The term “autosomal dominant” is used herein to refer to a single, abnormal gene on one of the autosomal chromosomes (one of the first 22 “non-sex” chromosomes) from either parent which can cause certain diseases. One of the parents will usually have the disease (as the gene is dominant) in this mode of inheritance. Only one parent must have an abnormal gene in order for the offspring to inherit the disease.

The present invention relates to animal models for hereditary autosomal dominant diseases. The models of the present invention can be used as model for hereditary autosomal dominant diseases as known from humans. Animal models for human diseases and especially those diseases such as the autosomal dominant diseases which develop over a long period of time, having a late onset in life are very useful in order to gain information on the onset, progression and treatment regime of individuals suffering from such type of diseases. It is appreciated that the animal models are non-human animals. In one aspect of the invention the non-human animal model for a hereditary autosomal dominant disease is a model wherein the non-human animal model expresses at least one phenotype associated with said hereditary autosomal dominant disease obtained by at least one genetic determinant. In another aspect of the invention the non-human animal model for a hereditary autosomal dominant disease is a model wherein the non-human animal model expresses at least one phenotype associated with said hereditary autosomal dominant disease obtained by sperm-mediated gene transfer.

It is appreciated that the non-human animal model may be obtained by the use of at least one, two, three, four, five, six, seven, eight, nine or ten genetic determinants. The genetic determinants of a given autosomal dominant disease whether in the form of DNA, RNA or protein as described herein may be combined in one animal model in order to obtain a strong phenotype of an autosomal dominant disease.

Autosomal dominant diseases are as described elsewhere herein diseases that are normally inherited through the non-sex chromosomes from one of the parents. Autosomal dominant diseases comprise diseases known as protein conformation diseases, neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS), Alzheimer’s disease, Parkinson’s disease, diseases related to Trinucleotide Repeats for example huntington’s chorea, but also conditions related to dyschondroplasia.

Protein conformation diseases are one type of neurodegenerative diseases in which protein folding disorders occur. The protein misfolding of specific proteins can be observed in affected neuronal tissue. Protein conformation diseases according to the present invention are ALS, Alzheimer’s disease, Parkinson’s disease, diseases associated with trinucleotide repeats and Huntington’s chorea.

#### ALS

In one embodiment the non-human animal model expresses at least one phenotype associated with ALS. In a particular aspect the non-human animal model is a pig model expressing at least one phenotype associated with ALS.

“Amyotroph lateral sclerosis (ALS)” is used herein to refer to any neurodegenerative disease that usually attacks both upper and lower motor neurons and causes degeneration throughout the brain and spinal cord.

Physicians have limited choices for treating ALS. At this time, Riluzole® is the only drug that has been approved by the FDA for treatment of ALS. In clinical trials, Riluzole® has shown a slight benefit in modestly increasing survival time of patients suffering from ALS.

Amyotrophic lateral Sclerosis (ALS) is the most common motor neurodegenerative disease characterised by a progressive loss of motor neurons in the spinal cord, brain stem, and motor cortex, causing weakness, muscular wasting and paresis, ultimately leading to death. Symptoms of the disease constitute weakness, stiffness, abnormal reflexes, fasciculations, cramps and atrophy. However, especially in the early phases of the disease, ALS can be difficult to diagnose since all symptoms are rarely present at that stage [1].

A common first symptom is a painless weakness in a hand, foot, arm or leg, which occurs in more than half of all cases. Other early symptoms include swallowing or walking difficulty. The biological mechanisms that cause ALS are only partially understood. One known cause of ALS is a mutation of a specific human gene: The SOD1 gene. This mutation is believed to make a defective protein that is toxic to motor nerve cells. The SOD1 mutation, however, accounts for only 1 or 2 percent of ALS cases, or 20 percent of the familial (inherited) cases. Familial ALS represents between five to 10 percent of all cases—the remaining cases seemingly arise spontaneously and attacks previously healthy adults.

The present invention relates to the production of a non-human animal model for ALS. The below Table 1 shows mutations which are associated with ALS in humans. According to the present invention any of the in table 1 listed mutations and substitutions as known from humans are embodiments of the present invention. Thus, the mutated forms of the porcine homolog of the human SOD1 and/or human SOD1 genes/cDNA, RNA and/or protein or parts thereof may comprise any of the listed mutations in order to produce a non-human animal model for ALS and in particular a pig model for ALS. It is appreciated that at least one or more mutations

may be introduced into the porcine homolog of the human SOD1 and/or human SOD1 genes/cDNA, RNA and/or pro

tein or parts thereof. Any number of the listed mutations may be used in combination.

TABLE 1

| Location | Codon | Mutation                  | Mutation                  | Mutation                  | Mutation | Mutation | Mutation |
|----------|-------|---------------------------|---------------------------|---------------------------|----------|----------|----------|
| exon 1   | 4     | Ala4Ser                   | Ala4Thr                   | Ala4Val                   |          |          |          |
| exon 1   | 6     | Cys6Phe                   | Cys6Gly                   |                           |          |          |          |
| exon 1   | 7     | Val7Glu                   |                           |                           |          |          |          |
| exon 1   | 8     | Leu8Val                   | Leu8Gln                   |                           |          |          |          |
| exon 1   | 10    | Gly10Val                  |                           |                           |          |          |          |
| exon 1   | 12    | Gly12Arg                  |                           |                           |          |          |          |
| exon 1   | 14    | Val14Met                  | Val14Gly                  |                           |          |          |          |
| exon 1   | 16    | Gly16Ser                  | Gly16Ala                  |                           |          |          |          |
| exon 1   | 19    | Asn19Ser                  |                           |                           |          |          |          |
| exon 1   | 20    | Phe20Cys                  |                           |                           |          |          |          |
| exon 1   | 21    | Glu21Lys                  | Glu21Gly                  |                           |          |          |          |
| exon 1   | 22    | Gln22Leu                  |                           |                           |          |          |          |
| intron 1 |       | 319t > a                  |                           |                           |          |          |          |
| exon 2   | 37    | Gly37Arg                  |                           |                           |          |          |          |
| exon 2   | 38    | Leu38Val                  | Leu38Arg                  |                           |          |          |          |
| exon 2   | 40    | Glu40Gly                  |                           |                           |          |          |          |
| exon 2   | 41    | Gly41Ser                  | Gly41Asp                  |                           |          |          |          |
| exon 2   | 43    | His43Arg                  |                           |                           |          |          |          |
| exon 2   | 45    | Phe45Cys                  |                           |                           |          |          |          |
| exon 2   | 46    | His46Arg                  |                           |                           |          |          |          |
| exon 2   | 47    | Val47Phe                  |                           |                           |          |          |          |
| exon 2   | 48    | His48Arg                  | His48Gln                  |                           |          |          |          |
| exon 2   | 49    | Glu49Lys                  |                           |                           |          |          |          |
| exon 2   | 54    | Thr54Arg                  |                           |                           |          |          |          |
| exon 3   | 57    | Cys57Arg                  |                           |                           |          |          |          |
| exon 3   | 59    | Ser59Ile                  |                           |                           |          |          |          |
| exon 3   | 65    | Asn65Ser                  |                           |                           |          |          |          |
| exon 3   | 67    | Leu67Arg                  |                           |                           |          |          |          |
| exon 3   | 72    | Gly72Cys                  | Gly72Ser                  |                           |          |          |          |
| exon 3   | 76    | Asp76Tyr                  | Asp76Val                  |                           |          |          |          |
| exon 4   | 80    | His80Arg                  |                           |                           |          |          |          |
| exon 4   | 84    | Leu84Val                  | Leu84Phe                  |                           |          |          |          |
| exon 4   | 85    | Gly85Arg                  |                           |                           |          |          |          |
| exon 4   | 86    | Asn86Asp                  | Asn86Ser                  |                           |          |          |          |
| exon 4   | 87    | Val87Met                  | Val87Ala                  |                           |          |          |          |
| exon 4   | 89    | Ala89Thr                  | Ala89Val                  |                           |          |          |          |
| exon 4   | 90    | Asp90Ala                  | Asp90Val                  |                           |          |          |          |
| exon 4   | 93    | Gly93Cys                  | Gly93Arg                  | Gly93Ser                  | Gly93Asp | Gly93Ala | Gly93Val |
| exon 4   | 95    | Ala95Thr                  |                           |                           |          |          |          |
| exon 4   | 96    | Asp96Asn                  |                           |                           |          |          |          |
| exon 4   | 97    | Val97Met                  |                           |                           |          |          |          |
| exon 4   | 100   | Glu100Lys                 | Glu100Gly                 |                           |          |          |          |
| exon 4   | 101   | Asp101His                 | Asp101Asn                 | Asp101Gly                 |          |          |          |
| exon 4   | 104   | Ile104Phe                 |                           |                           |          |          |          |
| exon 4   | 105   | Ser105Leu                 |                           |                           |          |          |          |
| exon 4   | 106   | Leu106Val                 |                           |                           |          |          |          |
| exon 4   | 108   | Gly108Val                 |                           |                           |          |          |          |
| exon 4   | 112   | Ile112Thr                 | Ile112Met                 |                           |          |          |          |
| exon 4   | 113   | Ile113Phe                 | Ile113Thr                 |                           |          |          |          |
| exon 4   | 114   | Gly114Ala                 |                           |                           |          |          |          |
| exon 4   | 115   | Arg115Gly                 |                           |                           |          |          |          |
| exon 4   | 116   | Thr116Arg                 |                           |                           |          |          |          |
| exon 4   | 118   | Val118Leu<br>(GTG to TTG) | Val118Leu<br>(GTG to CTG) |                           |          |          |          |
| intron 4 |       | 1415t > g                 |                           |                           |          |          |          |
| exon 5   | 124   | Asp124Val                 | Asp124Gly                 |                           |          |          |          |
| exon 5   | 125   | Asp125His                 |                           |                           |          |          |          |
| exon 5   | 126   | Leu126STOP                | Leu126Ser                 |                           |          |          |          |
| exon 5   | 134   | Ser134Asn                 |                           |                           |          |          |          |
| exon 5   | 139   | Asn139His                 | Asn139Lys                 |                           |          |          |          |
| exon 5   | 140   | Ala140Gly                 |                           |                           |          |          |          |
| exon 5   | 141   | Gly141STOP                | Gly141Glu                 |                           |          |          |          |
| exon 5   | 144   | Leu144Ser                 | Leu144Phe<br>(TTG to TTC) | Leu144Phe<br>(TTG to TTT) |          |          |          |
| exon 5   | 145   | Ala145Thr                 | Ala145Gly                 |                           |          |          |          |
| exon 5   | 146   | Cys146Arg                 |                           |                           |          |          |          |
| exon 5   | 147   | Gly147Arg                 |                           |                           |          |          |          |
| exon 5   | 148   | Val148Ile                 | Val148Gly                 |                           |          |          |          |
| exon 5   | 149   | Ile149Thr                 |                           |                           |          |          |          |
| exon 5   | 151   | Ile151Thr                 | Ile151Ser                 |                           |          |          |          |

Furthermore two mutations in ALS 2 (Ala46delA and Leu623delCT) and three mutations in ALS4, SETX, (Thr3Ile, Leu389Ser, and Arg2136His) are associated with ALS.

Thus, in one aspect of the present invention the non-human animal model expressing at least one phenotype associated with ALS due to the introduction of at least one genetic determinant, wherein the at least one genetic determinant is a gene or DNA or fragment thereof, and/or RNA or fragment thereof and/or protein or part thereof of the human SOD1 gene, mRNA and/or protein (see SEQ ID NO:1, SEQ ID NO:2) comprises at least one mutation yielding the acid mutations as described in table 1, or as described above for ALS 2 (Ala46delA and Leu623delCT) and three mutations in ALS4, SETX, (Thr3Ile, Leu389Ser, and Arg2136His), all associated with ALS.

Similarly, in one embodiment the non-human animal model expressing at least one phenotype associated with ALS due to the introduction of at least one genetic determinant, wherein the genetic determinant is a gene or DNA or fragment thereof, and/or RNA or fragment thereof and/or protein or part thereof of the porcine SOD1 gene, mRNA and/or protein (see SEQ ID NO:3, SEQ ID NO:4 or fragments or parts thereof) comprising at least one mutation yielding the amino acid mutations as described in table 1 or as described above for ALS 2 (Ala46delA and Leu623delCT) and three mutations in ALS4, SETX, (Thr3Ile, Leu389Ser, and Arg2136His), all associated with ALS. It is appreciated that the at least one mutation is present in the gene fragment or DNA fragment, RNA fragment or protein part. In particular the mutated porcine SOD1 cDNA with SEQ ID NO: 5 is used to produce a pig model for ALS.

The non-human animal model for ALS may be generated by introduction of said at least one genetic determinant into a target cell by any method available to the skilled person, for example by injection into the target cell, or by virus-mediated transfer or any method suitable as known by the skilled person.

In one particular embodiment the non-human animal model for ALS is generated by sperm mediated gene transfer.

The present invention discloses a pig model for ALS which in one embodiment is produced by sperm mediated gene transfer of the mutated porcine SOD1 (SEQ ID NO:5) as described elsewhere herein. However, the pig model for ALS may also be produced by introducing the mutated porcine SOD1 (SEQ ID NO: 5) or protein expressed (SEQ ID NO:6) thereof into a target cell.

It is appreciated that at least one mutation yielding the amino acid mutation of SOD1 in the human SOD1 as listed in table 1 or as described above for ALS 2 (Ala46delA and Leu623delCT) and three mutations in ALS4, SETX, (Thr3Ile, Leu389Ser, and Arg2136His), all associated with ALS are comprised in the human or porcine SOD1 gene or DNA, RNA or proteins of the present invention, such as for example at least two mutations, at least three mutations, at least four mutations, at least five mutations, at least six mutations, at least seven mutations, at least eight mutations, at least ten mutations, at least fifteen mutations yielding the amino acid mutation of SOD1 of table 1 or as described above for ALS 2 (Ala46delA and Leu623delCT) and three mutations in ALS4, SETX, (Thr3Ile, Leu389Ser, and Arg2136His), all associated with ALS.

The non-human animal model for ALS, in particular the pig model for ALS, will typically develop at least one of the symptoms described above such as weakness, stiffness, abnormal reflexes, fasciculations, cramps and atrophy. A common first symptom is a painless weakness in a leg, which

occurs in more than half of all cases. Other early symptoms include swallowing or walking difficulty. Furthermore, histopathology performed on a biopsy as described in the examples, herein can be used to diagnose the animal model with ALS. The analysis of the motor neurons for the presence aggregates, or even loss of the motor neurons are also characteristics of ALS.

#### Alzheimer's Disease

In another aspect of the present invention the non-human animal model expresses at least one phenotype associated with Alzheimer's disease. In a particular aspect the non-human animal model is a pig model expressing at least one phenotype associated with Alzheimer's disease.

Alzheimer's disease" is used herein to refer to any neurodegenerative brain disorder characterized by progressive memory loss and severe dementia in advanced cases. Alzheimer's disease is associated with certain abnormalities in brain tissue, involving a particular protein, beta-amyloid. Memory impairment is a necessary feature for the diagnosis of this type of dementia. Change in one of the following areas must also be present: language, decision-making ability, judgment, attention, and other areas of mental function and personality.

The rate of progression is different for each person. If Alzheimer's disease develops rapidly, it is likely to continue to progress rapidly. If it has been slow to progress, it will likely continue on a slow course. There are two types of Alzheimer's disease—early onset and late onset. In early onset Alzheimer's disease, symptoms first appear before age 60. Early onset Alzheimer's disease is much less common, accounting for only 5-10% of cases. However, it tends to progress rapidly.

Early onset disease can run in families and involves autosomal dominant, inherited mutations that may be the cause of the disease. So far, three early onset genes have been identified. Late onset Alzheimer's disease, the most common form of the disease, develops in people 60 and older and is thought to be less likely to occur in families. Late onset Alzheimer's disease may run in some families, but the role of genes is less direct and definitive. These genes may not cause the problem itself, but simply increase the likelihood of formation of plaques and tangles or other Alzheimer's disease-related pathologies in the brain.

The cause of Alzheimer's disease is not entirely known but is thought to include both genetic and environmental factors. A diagnosis of Alzheimer's disease is made based on characteristic symptoms and by excluding other causes of dementia. The only way to validate a case of Alzheimer's disease is by microscopic examination of a sample of brain tissue after death.

The brain tissue shows "neurofibrillary tangles" (twisted fragments of protein within nerve cells that clog up the cell), "neuritic plaques" (abnormal clusters of dead and dying nerve cells, other brain cells, and protein), and "senile plaques" (areas where products of dying nerve cells have accumulated around protein). Although these changes occur to some extent in all brains with age, there are many more of them in the brains of people with Alzheimer's disease.

The destruction of nerve cells (neurons) leads to a decrease in neurotransmitters (substances secreted by a neuron to send a message to another neuron). The correct balance of neurotransmitters is critical to the brain. By causing both structural and chemical problems in the brain, Alzheimer's disease appears to disconnect areas of the brain that normally work together.

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The following human genes are linked to Alzheimer's disease:

Presenilin 1 (PSEN1, NM\_000021),

Presenilin 2 (PSEN2, NM\_000447),

Amyloid beta precursor protein (APP, NM\_000484)

The below indicated substitutions are believed to be relevant regarding transgenic porcine models for Alzheimer's disease.

TABLE 2

| Mutations causing Alzheimer's disease in APP (NM_000484) |                     |
|----------------------------------------------------------|---------------------|
| Mutation #                                               | Mutation            |
| 1                                                        | Duplication of APP  |
| 2                                                        | LysMet670/671AsnLeu |
| 3                                                        | Ala673Thr           |
| 4                                                        | Asp678Asn           |
| 5                                                        | Ala692Gly           |
| 6                                                        | Glu693Lys           |
| 7                                                        | Glu693Gln           |
| 8                                                        | Glu693Gly           |
| 9                                                        | Asp694Asn           |
| 10                                                       | Leu705Val           |
| 11                                                       | Ala713Thr           |
| 12                                                       | Ala713Val           |
| 13                                                       | Thr714Ala           |
| 14                                                       | Thr714Ile           |
| 15                                                       | Val715Ala           |
| 16                                                       | Ile716Thr           |
| 17                                                       | Val717Ile           |
| 18                                                       | Val717Leu           |
| 19                                                       | Val717Phe           |
| 20                                                       | Val717Gly           |
| 21                                                       | Leu723Pro           |

TABLE 3

| Mutations causing Alzheimer's disease in PSEN2 (NM_000447) |           |
|------------------------------------------------------------|-----------|
| Mutation #                                                 | Mutation  |
| 1                                                          | Arg62His  |
| 2                                                          | Thr122Pro |
| 3                                                          | Ser130Leu |
| 4                                                          | Asn141Ile |
| 5                                                          | Val148Ile |
| 6                                                          | Gln228Leu |
| 7                                                          | Met239Ile |
| 8                                                          | Met239Val |
| 9                                                          | Thr430Met |
| 10                                                         | Asp439Ala |

TABLE 4

| Mutations causing Alzheimer's disease in PSEN1 (NM_000021) |                 |
|------------------------------------------------------------|-----------------|
| Mutation #                                                 | Mutation        |
| 1                                                          | Ala79Val        |
| 2                                                          | Val82Leu        |
| 3                                                          | delIle83/Met84  |
| 4                                                          | Leu85Pro        |
| 5                                                          | Val89Leu        |
| 6                                                          | Cys92Ser        |
| 7                                                          | Val94Met        |
| 8                                                          | Val96Phe        |
| 9                                                          | Phe105Ile       |
| 10                                                         | Phe105Leu       |
| 11                                                         | Leu113Gln       |
| 12                                                         | Leu113Pro       |
| 13                                                         | Intron4; InsTAC |
| 14                                                         | Tyr115Asp       |
| 15                                                         | Tyr115Cys       |

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TABLE 4-continued

| Mutations causing Alzheimer's disease in PSEN1 (NM_000021) |            |
|------------------------------------------------------------|------------|
| Mutation #                                                 | Mutation   |
| 16                                                         | Tyr115Asp  |
| 17                                                         | Thr116Asn  |
| 18                                                         | Thr116Ile  |
| 19                                                         | Pro117Ser  |
| 20                                                         | Pro117Arg  |
| 21                                                         | Pro117Leu  |
| 22                                                         | Glu120Lys  |
| 23                                                         | Glu120Asp  |
| 24                                                         | Glu123Lys  |
| 25                                                         | Asn135Asp  |
| 26                                                         | Asn135Ser  |
| 27                                                         | Met139Val  |
| 28                                                         | Met139Lys  |
| 29                                                         | Met139Thr  |
| 30                                                         | Met139Ile  |
| 31                                                         | Ile143Phe  |
| 32                                                         | Ile143Asn  |
| 33                                                         | Ile143Thr  |
| 34                                                         | Ile143Met  |
| 35                                                         | Met146Leu  |
| 36                                                         | Met146Val  |
| 37                                                         | Met146Leu  |
| 38                                                         | Met146Ile  |
| 39                                                         | Thr147Ile  |
| 40                                                         | Leu153Val  |
| 41                                                         | Tyr154Asn  |
| 42                                                         | Tyr154Cys  |
| 43                                                         | InsPhe/Ile |
| 44                                                         | His163Tyr  |
| 45                                                         | His163Arg  |
| 46                                                         | Trp165Gly  |
| 47                                                         | Trp165Cys  |
| 48                                                         | Leu166Pro  |
| 49                                                         | Leu166Arg  |
| 50                                                         | Del_Ile197 |
| 51                                                         | Ser169Pro  |
| 52                                                         | Ser170Phe  |
| 53                                                         | Leu171Pro  |
| 54                                                         | Leu173Trp  |
| 55                                                         | Leu174Met  |
| 56                                                         | Leu174Arg  |
| 57                                                         | Phe177Leu  |
| 58                                                         | Phe177Ser  |
| 59                                                         | Ser178Pro  |
| 60                                                         | Gly183Val  |
| 61                                                         | Glu184Asp  |
| 62                                                         | Gly206Ser  |
| 63                                                         | Gly206Asp  |
| 64                                                         | Gly206Ala  |
| 65                                                         | Gly206Val  |
| 66                                                         | Gly209Val  |
| 67                                                         | Gly209Arg  |
| 68                                                         | Gly209Glu  |
| 69                                                         | Ile213Leu  |
| 70                                                         | Ile213Phe  |
| 71                                                         | Ile213Thr  |
| 72                                                         | His214Tyr  |
| 73                                                         | Gly217Asp  |
| 74                                                         | Leu219Phe  |
| 75                                                         | Leu219Pro  |
| 76                                                         | Gln222Arg  |
| 77                                                         | Gln222His  |
| 78                                                         | Leu226Arg  |
| 79                                                         | Ile229Phe  |
| 80                                                         | Ala231Thr  |
| 81                                                         | Ala231Val  |
| 82                                                         | Met233Leu  |
| 83                                                         | Met233Val  |
| 84                                                         | Met233Thr  |
| 85                                                         | Leu235Val  |
| 86                                                         | Leu235Pro  |
| 87                                                         | Phe237Leu  |
| 88                                                         | Ala246Glu  |
| 89                                                         | Leu250Val  |
| 90                                                         | Leu250Ser  |
| 91                                                         | Tyr256Ser  |

TABLE 4-continued

| Mutations causing Alzheimer's disease in PSEN1 (NM_000021) |                       |
|------------------------------------------------------------|-----------------------|
| Mutation #                                                 | Mutation              |
| 92                                                         | Ala260Val             |
| 93                                                         | Val261Phe             |
| 94                                                         | Leu262Phe             |
| 95                                                         | Cys263Arg             |
| 96                                                         | Cys263Phe             |
| 97                                                         | Pro264Leu             |
| 98                                                         | Pro267Ser             |
| 99                                                         | Pro267Leu             |
| 100                                                        | Arg269Gly             |
| 101                                                        | Arg269His             |
| 102                                                        | Leu271Val             |
| 103                                                        | Val272Ala             |
| 104                                                        | Glu273Ala             |
| 105                                                        | Thr274Arg             |
| 106                                                        | Arg278Lys             |
| 107                                                        | Arg278Thr             |
| 108                                                        | Glu280Ala             |
| 109                                                        | Glu280Gly             |
| 110                                                        | Leu282Val             |
| 111                                                        | Leu282Arg             |
| 112                                                        | Pro284Leu             |
| 113                                                        | Ala285Val             |
| 114                                                        | Leu286Val             |
| 115                                                        | Deletions in intron 8 |
| 116                                                        | InsArg(g63786_63787)  |
| 117                                                        | Thr354Ile             |
| 118                                                        | Arg358Gln             |
| 119                                                        | Ser365Tyr             |
| 120                                                        | Arg377Met             |
| 121                                                        | Gly378Glu             |
| 122                                                        | Gly378Val             |
| 123                                                        | Leu381Val             |
| 124                                                        | Gly384Ala             |
| 125                                                        | Phe386Ser             |
| 126                                                        | Ser390Ile             |
| 127                                                        | Val391Phe             |
| 128                                                        | Leu392Val             |
| 129                                                        | Leu392Pro             |
| 130                                                        | Gly394Val             |
| 131                                                        | Asn405Ser             |
| 132                                                        | Ala409The             |
| 133                                                        | Cys410Tyr             |
| 134                                                        | Leu418Phe             |
| 135                                                        | Leu424His             |
| 136                                                        | Leu424Arg             |
| 137                                                        | Ala426Pro             |
| 138                                                        | Ala431Glu             |
| 139                                                        | Ala431Val             |
| 140                                                        | Ala434Cys             |
| 141                                                        | Leu435Phe             |
| 142                                                        | Pro436Ser             |
| 143                                                        | Pro436Gln             |
| 144                                                        | Ile439Val             |
| 145                                                        | DelThr440             |

Thus, in one embodiment the non-human animal model expressing at least one phenotype associated with Alzheimer's disease due to the introduction of at least one genetic determinant, wherein the at least one genetic determinant is a gene or DNA or fragment thereof, and/or RNA or fragment thereof and/or protein or part thereof of the human PSEN1 gene, mRNA and/or protein (see SEQ ID NO:7, SEQ ID NO:8), comprises at least one mutation yielding the amino acid mutations as described in table 4.

Similarly, in one embodiment the non-human animal model expressing at least one phenotype associated with Alzheimer's disease due to the introduction of at least one genetic determinant, wherein the genetic determinant is a gene or DNA or fragment thereof, and/or RNA or fragment thereof and/or protein or part thereof of the porcine PSEN1 gene, mRNA and/or protein (see SEQ ID NO:9, SEQ ID NO:10) or fragments or parts thereof, respectively) compris-

ing at least one mutation yielding the amino acid mutations as described in table 4. It is appreciated that the at least one mutation is present in the gene fragment or DNA fragment, RNA fragment or protein part. In particular the mutated porcine PSEN1 protein with SEQ ID NO: 11 is used to produce a pig model for Alzheimer's disease.

The non-human animal model for ALS may be generated by introduction of said at least one genetic determinant into a target cell by any method available to the skilled person, for example by injection into the target cell, or by virus-mediated transfer or any method suitable as known by the skilled person.

In one particular embodiment the non-human animal model for Alzheimer's disease is generated by sperm mediated gene transfer.

According to the present invention a pig model for Alzheimer's disease is in one embodiment produced by sperm mediated gene transfer of the mutated porcine PSEN1 as described elsewhere herein. However, the pig model for Alzheimer's disease may also be produced by introducing the mutated PSEN1 or protein expressed thereof ((SEQ ID NO: 11) into a target cell.

Moreover, in one embodiment the non-human animal model expressing at least one phenotype associated with Alzheimer's disease due to the introduction of at least one genetic determinant, wherein the genetic determinant is a gene or DNA or fragment thereof, and/or RNA or fragment thereof and/or protein or part thereof of the human PSEN2 gene, mRNA and/or protein (see SEQ ID NO:12, SEQ ID NO:13) comprises at least one mutation yielding the amino acid mutations as described in table 3.

Similarly, in one embodiment the non-human animal model expressing at least one phenotype associated with Alzheimer's disease due to the introduction of at least one genetic determinant, wherein the genetic determinant is a gene or DNA or fragment thereof, and/or RNA or fragment thereof and/or protein or part thereof of the porcine PSEN2 gene, mRNA and/or protein corresponding to SEQ ID NO:14, SEQ ID NO:15, or fragments or parts thereof, respectively) fitted with at least one mutation yielding the amino acid mutations as described in table 3. It is appreciated that the at least one mutation is present in the gene fragment or DNA fragment, RNA fragment or protein part. In particular the mutated porcine PSEN2 DNA with SEQ ID NO: 16 is used to produce a pig model for Alzheimer's disease.

The non-human animal model for ALS may be generated by introduction of said at least one genetic determinant into a target cell by any method available to the skilled person, for example by injection into the target cell, or by virus-mediated transfer or any method suitable as known by the skilled person.

In one particular embodiment the non-human animal model for Alzheimer's disease is generated by sperm mediated gene transfer.

According to the present invention a pig model for Alzheimer's disease is in one embodiment produced by sperm mediated gene transfer of the mutated porcine PSEN1 as described elsewhere herein. However, the pig model for Alzheimer's disease may also be produced by introducing the mutated PSEN1 or protein expressed thereof into a target cell (SEQ ID NO: 16).

Furthermore, in yet another embodiment the non-human animal model expressing at least one phenotype associated with Alzheimer's disease due to the introduction of at least one genetic determinant, wherein the genetic determinant is a gene or DNA or fragment thereof, and/or RNA or fragment thereof and/or protein or part thereof of the human APP gene,

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mRNA and/or protein (SEQ ID NO:17, SEQ ID NO:18) comprises at least one mutation yielding the amino acid mutations as described in table 2. Similarly, in one embodiment the non-human animal model expressing at least one phenotype associated with Alzheimer's disease due to the introduction of at least one genetic determinant, wherein the genetic determinant is a gene or DNA or fragment thereof, and/or RNA or fragment thereof and/or protein or part thereof of the porcine APP gene, mRNA and/or protein corresponding to SEQ ID NO:19, SEQ ID NO:20, or fragments or parts thereof, comprising at least one mutation yielding the amino acid mutations as described in table 2. It is appreciated that the at least one mutation is present in the gene fragment or cDNA fragment, RNA fragment or protein part. In particular the mutated porcine APP DNA is used to produce a pig model for Alzheimer's disease.

The non-human animal model for Alzheimer's disease may be generated by introduction of said genetic determinant into a target cell by any method available to the skilled person, for example by injection into the target cell.

In one particular embodiment the non-human animal model for Alzheimer's disease is generated by sperm mediated gene transfer.

According to the present invention a pig model for Alzheimer's disease is in one embodiment produced by sperm mediated gene transfer of the mutated porcine APP as described elsewhere herein. However, the pig model for Alzheimer's disease may also be produced by introducing the mutated APP or protein expressed thereof into a target cell (SEQ ID NO: 21).

It is within the scope of the present invention that at least one mutation yielding the amino acid mutation homologous to the human PSEN1, PSEN2 and/or APP as listed in table 4, 3, and/or 2 is comprised in the human or porcine PSEN1, PSEN2 and/or APP gene or DNA, RNA or proteins of the present invention, such as for example at least two mutations, at least three mutations, at least four mutations, at least five mutations, at least six mutations, at least seven mutations, at least eight mutations, at least ten mutations, at least fifteen mutations yielding the amino acid mutation homologous to the human PSEN1, PSEN2 and/or APP as listed in table 4, 3, and/or 2. It is appreciated that one or more of the genes and mutations thereof may be combined in an animal model for example a pig model for Alzheimer's disease.

The non-human animal model for Alzheimer's disease, in particular the pig model for Alzheimer's disease, will typically develop at least one of the symptoms described above such as progressive memory loss and severe dementia in advanced cases which can be monitored by behavioural studies. Evidence also exists for the impairment of olfactory sense which can be monitored by behavioural changes. Furthermore, scannings of the brain of the animal models by magnetic resonance and/or positron emission tomography can also be employed to determine whether the animal model is indicative for Alzheimer's disease.

#### Parkinson's Disease

In one embodiment of the present invention the non-human animal model expresses at least one phenotype associated with Parkinson's disease. In a particular aspect the non-human animal model is a pig model expressing at least one phenotype associated with Parkinson's disease.

"Parkinson's disease" is used herein to refer to an inherited condition usually associated with the following symptoms—all of which result from the loss of dopamine-producing brain cells: tremor or trembling of the arms, jaw, legs, and face;

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stiffness or rigidity of the limbs and trunk; bradykinesia—slowness of movement; postural instability, or impaired balance and coordination.

Parkinson's disease (PD) is a common progressive neurodegenerative disease affecting 1-2% of the population over 60 years of age. The number of PD affected individuals reaches a maximum value between 70 and 79 years of age with a mean age of onset between 60 and 65 years (1). The cardinal clinical symptoms of PD are resting tremor, bradykinesia, rigidity and postural instability. The pathological manifestations of PD are characterized by degeneration of dopaminergic neurons in the substantia nigra pars compacta and the presence of so called Lewy bodies in degenerating neurons. Lewy bodies are cytoplasmic protein inclusions and the main constituent is the protein  $\alpha$ -synuclein. Lewy bodies are required for a pathological diagnosis of PD but can also be observed in other neurodegenerative diseases. Degeneration of dopaminergic neurons results in decreased production of dopamine and the lack of this signal substance is responsible for bradykinesia and rigidity. The etiology of PD is largely unknown but is probably due to both genetic and environmental factors. Impaired mitochondrial function, changes in protein sorting by the ubiquitin-proteasome pathway and facilitated apoptosis may all represent factors associated with development of PD (2). Environmental factors suggested are exposure to pesticides and heavy metals (3).

Most cases of PD are sporadic but 5-10% of cases are caused by genetic mutations.

Several transgenic animal models of PD have been established including nematodes (*C. elegans*), *Drosophila*, mice and rats and different PD associated genes. Several limitations to the mice models have been observed, including the absence of loss of nigrostriatal dopaminergic neurons in some of the models suggesting that a better animal model would be of advantage regarding the study of the factors involved in PD pathology and underlying mechanisms.

The following genes are linked to Parkinson's disease:

Alpha synuclein (SNCA, NM\_000345),

Ubiquitin C-terminal hydrolase (UCHL1, NM\_004181),

Leucine rich repeat kinase (LRRK2, NM\_198578).

The below indicated substitutions are believed to be relevant regarding transgenic porcine models for Parkinson's disease.

TABLE 5

| Mutations causing Parkinson's disease in SNCA (NM_000345) |          |
|-----------------------------------------------------------|----------|
| Mutation #                                                | Mutation |
| 1                                                         | Ala30Pro |
| 2                                                         | Glu46Lys |
| 3                                                         | Ala53Thr |

TABLE 6

| Mutations causing Parkinson's disease in UCHL1 (NM_004181) |          |
|------------------------------------------------------------|----------|
| Mutation #                                                 | Mutation |
| 1                                                          | Ser18Tyr |
| 2                                                          | Ile93Met |

TABLE 7

| Putative pathogenic mutations causing Parkinson's disease in LRRK2 (NM_198578) |             |
|--------------------------------------------------------------------------------|-------------|
| Mutation #                                                                     | Mutation    |
| 1                                                                              | Arg793Met   |
| 2                                                                              | Gln930Arg   |
| 3                                                                              | Arg1067Gln  |
| 4                                                                              | Ser1096Cys  |
| 5                                                                              | Ser1228Thr  |
| 6                                                                              | Ile1371Val  |
| 7                                                                              | Arg1441His  |
| 8                                                                              | Arg11514Gln |
| 9                                                                              | Met1869Thr  |
| 10                                                                             | Arg1941His  |
| 11                                                                             | Thr2356Ile  |
| 12                                                                             | Gly2385Arg  |

One aspect of the present invention thus relates to a non-human animal model expressing at least one phenotype associated with Parkinson's disease due to the introduction of at least one genetic determinant, wherein the genetic determinant is a gene or DNA or fragment thereof, and/or RNA or fragment thereof and/or protein or part thereof of the human SNCA gene, mRNA and/or protein (SEQ ID NO:22, SEQ ID NO:23) comprises at least one mutation yielding the amino acid mutations as described in table 5.

Similarly, in one embodiment the non-human animal model expressing at least one phenotype associated with Parkinson's disease due to the introduction of at least one genetic determinant, wherein the genetic determinant is a gene or DNA or fragment thereof, and/or RNA or fragment thereof and/or protein or part thereof of the porcine SNCA gene, mRNA and/or protein corresponding to SEQ ID NO:24, SEQ ID NO:25 or fragments or parts thereof, respectively) comprising at least one mutation yielding the amino acid mutations as described in table 5. It is appreciated that the at least one mutation is present in the gene fragment or DNA fragment, RNA fragment or protein part. In particular the mutated porcine SNCA cDNA with SEQ ID NO: 26 is used to produce a pig model for Parkinson's disease.

The non-human animal model for ALS may be generated by introduction of said at least one genetic determinant into a target cell by any method available to the skilled person, for example by injection into the target cell, or by virus-mediated transfer or any method suitable as known by the skilled person.

In one particular embodiment the non-human animal model for Parkinson's disease is generated by sperm mediated gene transfer.

According to the present invention a pig model for Parkinson's disease is in one embodiment produced by sperm mediated gene transfer of the mutated porcine SNCA (SEQ ID NO:26) as described elsewhere herein. However, the pig model for Parkinson's disease may also be produced by introducing the mutated SNCA DNA (SEQ ID NO: 26) or protein expressed thereof into a target cell SEQ ID NO: 27).

Moreover, in one embodiment the non-human animal model expressing at least one phenotype associated with Parkinson's disease due to the introduction of at least one genetic determinant, wherein the genetic determinant is a gene or DNA or fragment thereof, and/or RNA or fragment thereof and/or protein or part thereof of the human UCHL1 gene, mRNA and/or protein (SEQ ID NO:28, SEQ ID NO:29) comprises at least one mutation yielding the amino acid mutations as described in table 6.

Similarly, in one embodiment the non-human animal model expressing at least one phenotype associated with Par-

kinson's disease due to the introduction of at least one genetic determinant, wherein the genetic determinant is a gene or DNA or fragment thereof, and/or RNA or fragment thereof and/or protein or part thereof of the porcine UCHL1 gene, mRNA and/or protein or fragments or parts thereof comprising at least one mutation yielding the amino acid mutations as described in table 6. It is appreciated that the at least one mutation is present in the gene fragment or DNA fragment, RNA fragment or protein part. In particular the mutated porcine UCHL1 DNA is used to produce a pig model for Parkinson's disease.

The non-human animal model for Parkinson's disease may be generated by introduction of said genetic determinant into a target cell by any method available to the skilled person, for example by injection into the target cell.

In one particular embodiment the non-human animal model for Parkinson's disease is generated by sperm mediated gene transfer.

According to the present invention a pig model for Parkinson's disease is in one embodiment produced by sperm mediated gene transfer of the mutated porcine UCHL1 as described elsewhere herein. However, the pig model for Parkinson's disease may also be produced by introducing the mutated UCHL1 or protein expressed thereof into a target cell.

Furthermore, in yet another embodiment the non-human animal model expressing at least one phenotype associated with Parkinson's disease due to the introduction of at least one genetic determinant, wherein the genetic determinant is a gene or DNA or fragment thereof, and/or RNA or fragment thereof and/or protein or part thereof of the human LRRK2 gene, mRNA and/or protein (SEQ ID NO:30, SEQ ID NO:31) comprises at least one mutation yielding the amino acid mutations as described in table 7.

Similarly, in one embodiment the non-human animal model expressing at least one phenotype associated with Parkinson's disease due to the introduction of at least one genetic determinant, wherein the genetic determinant is a gene or DNA or fragment thereof, and/or RNA or fragment thereof and/or protein or part thereof of the porcine LRRK2 gene, mRNA and/or protein or fragments or parts thereof, respectively) fitted with at least one mutation yielding the amino acid mutations as described in table 7. It is appreciated that the at least one mutation is present in the gene fragment or DNA fragment, RNA fragment or protein part. In particular the mutated porcine LRRK2 DNA is used to produce a pig model for Parkinson's disease.

The non-human animal model for Parkinson's disease may be generated by introduction of said genetic determinant into a target cell by any method available to the skilled person, for example by injection into the target cell.

In one particular embodiment the non-human animal model for Parkinson's disease is generated by sperm mediated gene transfer.

According to the present invention a pig model for Parkinson's disease is in one embodiment produced by sperm mediated gene transfer of the mutated porcine LRRK2 as described elsewhere herein. However, the pig model for Alzheimer's disease may also be produced by introducing the mutated LRRK2 or protein expressed thereof into a target cell.

It is within the scope of the present invention that at least one mutation yielding the amino acid mutation homologous to the human SNCA, UCHL1 and/or LRRK2 as listed in table 5, 6 and/or 7 is comprised in the human or porcine SNCA, UCHL1 and/or LRRK2 gene or DNA, RNA or proteins of the present invention, such as for example at mutations, at least

six mutations, at least seven mutations, at least eight mutations, at least ten mutations, at least fifteen mutations yielding the amino acid mutation homologous to the human SNCA, UCHL1 and/or LRRK2 as listed in table 5, 6 and/or 7. It is appreciated that one or more of the genes and mutations thereof may be combined in an animal model for example a pig model for Parkinson's disease.

The non-human animal model for Parkinson's disease, in particular the pig model for Parkinson's disease, will typically develop at least one of the symptoms described above such as symptoms—all of which result from the loss of dopamine-producing brain cells: tremor or trembling of the jaw, legs, and face, stiffness or rigidity of the limbs and trunk, bradykinesia—slowness of movement; postural instability, or impaired balance and coordination.

#### Trinucleotide Repeat (TNR) Disorders

In one embodiment of the present invention the non-human animal model expresses at least one phenotype associated with diseases related to trinucleotide repeat disorders. In a particular aspect the non-human animal model is a pig model expressing at least one phenotype associated with diseases related to trinucleotide repeat disorders.

Trinucleotide repeat disorders or expansion disorders are caused by stretches of DNA in a gene that contain the same trinucleotide sequence repeated many times. Unstable microsatellite repeats are found throughout all genomic sequences and TNRs constitute a subset of such unstable repeats.

Nucleotide repeat instability is associated with more than 40 inherited neurodegenerative, neuromuscular, and mental retardation disorders in humans [2,3]. The nucleotide repeat instability process is a dynamic process, where mutations continue to recur during meiosis and in mitotic tissue [3]. Long stretches of repeats are more likely to expand than short stretches of repeats and the length is correlated with age of onset and the severity of disease, a phenomena called anticipation [3]. Diseases caused by trinucleotide repeat (TNR) instability can be divided into two groups. In the first group the TNRs reside in the untranslated part of the affected genes. The untranslated TNR expansions, constituting either CTGs, CAGs, GAAs, or CGGs, result in an RNA gain-of-function that may alter the gene expression control of the affected genes or have cis and trans effects on splicing and gene regulation at the chromatin level [4-7]. Expanded noncoding TNRs have been identified as causative mutations in disorders including Friedreich ataxia, spinocerebellar ataxia 8 (SCA-8), SCA-12, myotonic dystrophy, and fragile-X syndromes [3].

In the second group the TNRs are located in the coding region of the transcript. This type of TNRs are translated in frame of the coding region and expansions include GAC encoding poly-asparagine, GCG encoding poly-alanine, and the most commonly identified CAG TNRs encoding poly-glutamine [3]. Expanded CAG TNRs, are identified as causative mutations in disorders, including SCA-1, SCA-2, SCA-3, SCA-6, SCA-7, SCA17, Huntington's disease, spinal and bulbar muscular atrophy (SBMA), and dentatorubral pallidoluysian atrophy (DRPLA). In these disorders cytoskeletal and vesicular functions are affected as well as the regulation of cellular gene expression due to the sequestering of transcriptional regulatory proteins.

The molecular mechanisms responsible for TNR instability are not completely elucidated. The degree of tissue-specific and inherited TNR instability is determined by both the specific cis-sequences within the affected genes and trans-functioning metabolic proteins as for example DNA repair proteins [3]. TNR instability probably involves the formation

of specific DNA structures during DNA replication, repair and recombination [8]. Slippage during DNA replication is the best characterized mechanism. The direction of DNA replication through the TNR tract also affects the stability [9-11]. In addition to the TNR itself, the sequence environment of the repeat contributes to the mechanism of instability, and, for example, similar CAG tract lengths show different stability depending on the genomic context [3, 12]. In the human population the length of TNR repeat tracts is polymorphic but stably transmitted [13]. Beyond a certain TNR length, which appears to be gene specific, the TNR tract becomes unstable [3]. An unstable TNR tract that has not yet expanded to a size sufficient for the full disease phenotype is called a premutation [2]. However, TNR expansions of the premutation size in for example FMR1 have been shown to result in a specific disease phenotype of late onset. The genetic instability of TNRs is related to the repeat tract length and expanded tracts have increased risk of being affected by a subsequent expanding mutation than the original tract [2, 3, 14]. Also TNR interruptions, as for example CAA triplets in CAG TNRs, play an important role conferring TNR stability and their absence predisposes alleles towards instability and pathological expansions [15]. A large level of somatic and transmitted instability is observed for premutation and fully expanded TNR tracts [2,3]. The fully expanded and disease causing TNR tracts can be composed of approximately twenty TNRs as observed in SCA-6 to several thousands as observed in for example myotonic dystrophy [2,3]. Interestingly, it was recently shown that an induced level of transcription promotes contraction of TNR tracts in human cells [16]. Furthermore, transgenic animal models of TNR instability also points out the importance for specific TNR flanking sequences to create TNR instability [9, 17, 18].

One embodiment of the present invention relates to a non-human animal model expressing at least one phenotype associated with myotonic dystrophy. In a particular aspect the non-human animal model is a pig model expressing at least one phenotype associated with myotonic dystrophy.

Myotonic dystrophy is caused by TNR in the 3'-UTR of the human myotonic dystrophy protein kinase gene, DMPK, where a CTG TNR is located [19-23]. The normal size of this TNR varies between 5 and 37. Expansions from above 50 to several thousand CTG repeats result in myotonic dystrophy.

One aspect of the present invention thus relates to a non-human animal model expressing at least one phenotype associated with myotonic dystrophy due to the introduction of at least one genetic determinant, wherein the genetic determinant is a gene or DNA or fragment thereof, and/or RNA or fragment thereof and/or protein or part thereof of the human myotonic dystrophy protein kinase gene, DMPK gene, mRNA and/or protein (SEQ ID NO:32, SEQ ID NO:33), wherein the number of CTG repeats is at least 40, 45, 50 or at least 60.

Similarly, in one embodiment the non-human animal model expressing at least one phenotype associated with myotonic dystrophy due to the introduction of a genetic determinant, wherein the genetic determinant is a gene or DNA or fragment thereof, and/or RNA or fragment thereof and/or protein or part thereof of the porcine homolog of the human DMPK gene, mRNA and/or protein or fragments or parts thereof, respectively), wherein the number of CTG repeats in the DNA is at least 40, 45, 50 or at least 60.

The non-human animal model for myotonic dystrophy may be generated by introduction of said genetic determinant into a target cell by any method available to the skilled person,

for example by injection into the target cell, or by virus-mediated transfer or any method suitable as known by the skilled person.

In one particular embodiment the non-human animal model for myotonic dystrophy is generated by sperm mediated gene transfer.

According to the present invention a pig model for myotonic dystrophy is in one embodiment produced by sperm mediated gene transfer of the human or porcine DMPK gene, mRNA and/or protein, wherein the number of CTG repeats in the DNA is at least 40, 45, 50 or at least 60. However, the pig model for myotonic dystrophy may also be produced by introducing the human or porcine DMPK gene, mRNA and/or protein, wherein the number of CTG repeats in the DNA is at least 40, 45, 50 or at least 60, or protein expressed thereof into a target cell.

The non-human animal model for myotonic dystrophy, in particular the pig model for myotonic dystrophy, will typically develop at least one of the symptoms such as generalized weakness and muscular wasting that affects the face and neck; difficulty with the feet that spreads to the legs, shoulders and hips. Other symptoms include a wasting of the muscles (muscular dystrophy), opacity of the lens of the eyes (cataracts), heart conduction defects and myotonia (difficulty in relaxing muscles).

#### Fragile X Syndrome

One embodiment of the present invention relates to a non-human animal model expressing at least one phenotype associated with fragile X syndrome. In a particular aspect the non-human animal model is a pig model expressing at least one phenotype associated with fragile X syndrome.

Fragile X syndrome is caused by repeats in the promoter region of the human FMR1 gene, 6 to 52 CGG repeats are normally present [24, 25]. Expansions in the range of 55 to 200 repeats result in the pre-mutation while the full mutation ranges from 200 to several thousand repeats resulting in fragile X syndrome. Fragile X syndrome may also be caused by CCG repeats in the TNR of the 5' end of the human FMR2 gene, wherein the number of repeats varies from 6 to 35 [26]. Expansions containing from 61 to 200 repeats result in the pre-mutation and expansions above 200 repeats result in the full mutation and the fragile X syndrome.

One aspect of the present invention thus relates to a non-human animal model expressing at least one phenotype associated with Fragile X syndrome due to the introduction of at least one genetic determinant, wherein the at least one genetic determinant is a gene or DNA or fragment thereof, and/or RNA or fragment thereof and/or protein or part thereof of the human FMR1 gene/cDNA, mRNA and/or protein (SEQ ID NO:34, SEQ ID NO:35) wherein the number of CGG repeats is at least 55, 60, 70 or at least 200, and/or of the human FMR2 gene/cDNA, mRNA and/or protein (SEQ ID NO:36, SEQ ID NO:37) wherein the number of CCG repeats is at least 61, 65, 70, 80 or at least 200,

Similarly, one embodiment relates to the non-human animal model expressing at least one phenotype associated with fragile X syndrome due to the introduction of at least one genetic determinant, wherein the at least one genetic determinant is a gene or DNA or fragment thereof, and/or RNA or fragment thereof and/or protein or part thereof of the porcine homolog of the human FMR1 gene/cDNA, mRNA and/or protein, wherein the number of CGG repeats is at least 55, 60, 70 or at least 200, and/or of the porcine homolog of the human FMR2 gene/cDNA, mRNA and/or protein, wherein the number of CCG repeats is at least 61, 65, 70, 80 or at least 200,

The non-human animal model for fragile X syndrome may be generated by introduction of said genetic determinant into

a target cell by any method available to the skilled person, for example by injection into the target cell.

In one particular embodiment the non-human animal model for fragile X syndrome is generated by sperm mediated gene transfer.

According to the present invention a pig model for fragile X syndrome is in one embodiment produced by sperm mediated gene transfer of the human or the porcine homolog of the human FMR1 gene/cDNA, mRNA and/or protein, fragments or part thereof, wherein the number of CGG repeats is at least 55, 60, 70 or at least 200, and/or the human or the porcine homolog of the human FMR2 gene/cDNA, mRNA and/or protein, fragment or part thereof, wherein the number of CCG repeats is at least 61, 65, 70, 80 or at least 200. However, the pig model for myotonic dystrophy may also be produced by introducing the human or porcine FMR1 gene/cDNA, mRNA and/or protein, fragments or part thereof, wherein the number of CGG repeats is at least 55, 60, 70 or at least 200, and/or the human or the porcine homolog of the human FMR2 gene/cDNA, mRNA and/or protein, fragment or part thereof, wherein the number of CCG repeats is at least 61, 65, 70, 80 or at least 200, or protein expressed thereof into a target cell.

The non-human animal model for fragile X syndrome, in particular the pig model for fragile X syndrome, will typically develop at least one of the symptoms associated with autism. Non-limiting examples of symptoms of autism is for example repetitive behaviour and impairment in social interaction. Spinocerebellar Ataxia

One embodiment of the present invention relates to a non-human animal model expressing at least one phenotype associated with spinocerebellar ataxia. In a particular aspect the non-human animal model is a pig model expressing at least one phenotype associated with spinocerebellar ataxia.

Spinocerebellar ataxia (SCA12) is caused by repeats in the within the 5'-UTR of the human PPP2R2B gene and the number of CAG repeats normally varies in size from 7 to 28 and in the expanded form from above 65 to 78 TNRs [27].

Spinocerebellar ataxia (SCA 1) is caused by CAG repeats in the ATX1 protein. The human SCA1 TNR region is characterized by the presence of 12 CAG repeats followed by two CAT repeats flanking a CAG triplet [28]. The CAG TNR prone to expand is normally composed of between 6 and 39 repeats and the expanded version consists of 41 to 81 repeats.

Spinocerebellar ataxia (SCA 2) is caused by TNR expansions affecting the ATX2 protein. This TNR normally consists of 15 to 30 CAG repeats and the expanded form ranges from 35 to 59 triplets [29].

Spinocerebellar ataxia (SCA 3) is caused by a CAG TNR expansion in the human ataxin-3 gene, wherein the presence of above 54 repeats results in ataxia whereas the normal number of CAG repeats varies between 12 and 36 [30-32].

Spinocerebellar ataxia (SCA6) is caused by TNR expansion in the CACNA1A voltage dependent calcium channel results in ataxia [33]. The normal number of TNRs is between 4 and 18 and expansions from 21 to 27 TNRs are disease causative.

Spinocerebellar ataxia (SCA7) is caused by TNR of the human SCA7 locus in the N-terminal end of the ataxin-7 protein, which is normally composed of 7 to 35 CAG repeats [34]. Disease causing expansions range from 37 to 200 repeats.

Spinocerebellar ataxia (SCA17) is caused by a CAG expansion in the TATA box binding protein (TBP) gene and results in the SCA17 phenotype resulting in ataxia [35]. The human TNR region is composed of two groups of CAG repeats separated by multiple CAA and CAG triplets. Expansions normally progress from the larger of the two CAG

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groups. The normal stretch of encoded poly-glutamines varies between 29 and 42 whereas poly-glutamine stretches from 47 to 55 have been identified in SCA17 patients.

One aspect of the present invention thus relates to a non-human animal model expressing at least one phenotype associated with Spinocerebellar ataxia due to the introduction of at least one genetic determinant, wherein the at least one genetic determinant is a gene or DNA or fragment thereof, and/or RNA or fragment thereof and/or protein or part thereof of the human PPP2R2B gene/cDNA, mRNA and/or protein (SEQ ID NO:38, SEQ ID NO:39), wherein the number of CAG repeats is at least 65, 70 or at least 75, and/or of the human ATX1 gene/cDNA, mRNA and/or protein (SEQ ID NO:40 SEQ ID NO:41), wherein the number of 12 CAG repeats followed by two CAT repeats flanking a CAG triplet is at least 41, 45, 50, 60, 70 or at least 80. The at least one genetic determinant may also be a gene or DNA or fragment thereof, and/or RNA or fragment thereof and/or protein or part thereof of the human ATX2 gene/cDNA, mRNA and/or protein (SEQ ID NO:42, SEQ ID NO:43), wherein the number of CAG repeats is at least 35, 40, 45, 50 or at least 55, and/or the at least one genetic determinant is a gene or DNA or fragment thereof, and/or RNA or fragment thereof and/or protein or part thereof of the human ataxin-3 gene/cDNA, mRNA and/or protein (SEQ ID NO:44, SEQ ID NO:45), wherein the number of CAG repeats is at least 54 and/or the at least one genetic determinant is a gene or DNA or fragment thereof, and/or RNA or fragment thereof and/or protein or part thereof of the human CACNA1A gene/cDNA, mRNA and/or protein (SEQ ID NO:46, SEQ ID NO:47), wherein the number of TNR expansions is at least 21, 22, 23, 24, 25, 26 or at least 27, or in the range of 21 to 27 repeats; and/or the at least one genetic determinant is a gene or DNA or fragment thereof, and/or RNA or fragment thereof and/or protein or part thereof of the human N-terminal end of the ataxin-7 protein encoding gene/cDNA, mRNA and/or protein (SEQ ID NO:48, SEQ ID NO:49), wherein the number of CAG expansions is at least 37, 45, 55, 65, or at least 100; and/or the at least one genetic determinant is a gene or DNA or fragment thereof, and/or RNA or fragment thereof and/or protein or part thereof of the human TATA box binding protein (TBP) gene/cDNA, mRNA and/or protein (SEQ ID NO:50, SEQ ID NO:51), wherein the number of poly-glutamine stretches as defined above is in the range of from 47 to 55 repeats.

Similarly, one embodiment relates to the non-human animal model expressing at least one phenotype associated with spinocerebellar ataxia due to the introduction of at least one genetic determinant, wherein the at least one genetic determinant is a gene or DNA or fragment thereof, and/or RNA or fragment thereof and/or protein or part thereof of the porcine homolog of the human PPP2R2B gene/cDNA, mRNA and/or protein, wherein the number of CAG repeats is at least 65, 70 or at least 75, and/or of the porcine homolog of the human ATX1 gene/cDNA, mRNA and/or protein, wherein the number of 12 CAG repeats followed by two CAT repeats flanking a CAG triplet is at least 41, 45, 50, 60, 70 or at least 80. The at least one genetic determinant may also be a gene or DNA or fragment thereof, and/or RNA or fragment thereof and/or protein or part thereof of the porcine homolog of the human ATX2 gene/cDNA, mRNA and/or protein, wherein the number of CAG repeats is at least 35, 40, 45, 50 or at least 55, and/or the at least one genetic determinant is a gene or DNA or fragment thereof, and/or RNA or fragment thereof and/or protein or part thereof of the porcine homolog of the human ataxin-3 gene/cDNA, mRNA and/or protein, wherein the number of CAG repeats is at least 54 and/or the at least one genetic determinant is a gene or DNA or fragment thereof,

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and/or RNA or fragment thereof and/or protein or part thereof of the porcine homolog of the human CACNA1A gene/cDNA, mRNA and/or protein, wherein the number of TNR expansions is at least 21, 22, 23, 24, 25, 26 or at least 27, or in the range of 21 to 27 repeats; and/or the at least one genetic determinant is a gene or DNA or fragment thereof, and/or RNA or fragment thereof and/or protein or part thereof of the porcine homolog of the human N-terminal end of the ataxin-7 protein encoding gene/cDNA, mRNA and/or protein, wherein the number of CAG expansions is at least 37, 45, 55, 65, or at least 100; and/or the at least one genetic determinant is a gene or DNA or fragment thereof, and/or RNA or fragment thereof and/or protein or part thereof of the porcine homolog of the human TATA box binding protein (TBP) gene/cDNA, mRNA and/or protein, wherein the number of poly-glutamine stretches as defined above is in the range of from 47 to 55 repeats.

The non-human animal model for spinocerebellar ataxia may be generated by introduction of said genetic determinant into a target cell by any method available to the skilled person, for example by injection into the target cell, or by virus-mediated transfer or any method suitable as known by the skilled person.

In one particular embodiment the non-human animal model for spinocerebellar ataxia is generated by sperm mediated gene transfer.

According to the present invention a pig model for spinocerebellar ataxia is in one embodiment produced by sperm mediated gene transfer of the human or the porcine homolog of the human PPP2R2B gene/cDNA, mRNA and/or protein, wherein the number of CAG repeats is at least 65, 70 or at least 75, and/or the porcine homolog of the human or the human ATX1 gene/cDNA, mRNA and/or protein, wherein the number of 12 CAG repeats followed by two CAT repeats flanking a CAG triplet is at least 41, 45, 50, 60, 70 or at least 80, and/or the human or the porcine homolog of the human ATX2 gene/cDNA, mRNA and/or protein, wherein the number of CAG repeats is at least 35, 40, 45, 50 or at least 55, and/or the human or the porcine homolog of the human ataxin-3 gene/cDNA, mRNA and/or protein, wherein the number of CAG repeats is at least 54 and/or the human or the porcine homolog of the human CACNA1A gene/cDNA, mRNA and/or protein, wherein the number of TNR expansions is at least 21, 22, 23, 24, 25, 26 or at least 27, or in the range of 21 to 27 repeats; and/or the human or the porcine homolog of the human N-terminal end of the ataxin-7 protein encoding gene/cDNA, mRNA and/or protein, wherein the number of CAG expansions is at least 37, 45, 55, 65, or at least 100; and/or the human or porcine homolog of the human TATA box binding protein (TBP) gene/cDNA, mRNA and/or protein, wherein the number of poly-glutamine stretches as defined above is in the range of from 47 to 55 repeats.

However, the pig model for spinocerebellar ataxia may also be produced by introducing the human or porcine homolog of PPP2R2B, ATX1, ATX2, ataxin-3, CACNA1A, ataxin-7 and/or TATA box binding protein (TBP) in any combination.

The non-human animal model for spinocerebellar ataxia, in particular the pig model for spinocerebellar ataxia, will typically develop at least one of the symptoms such as atrophy of the cerebellum which can be seen by magnetic resonance imaging and/or poor coordination of movement. Dentatorubral-Pallidoluysian Atrophy (DRPLA)

One embodiment of the present invention relates to a non-human animal model expressing at least one phenotype associated with DRPLA. In a particular aspect the non-human animal model is a pig model expressing at least one phenotype associated with DRPLA.

DRPLA is caused by CAG expansions within the human atrophin-1 gene results in dentatorubral-pallidoluysian atrophy (DRPLA) [36]. The normal range of repetitive CAG repeats is from 3 to 25, and in patients with DRPLA allele sizes have expanded to 49 to 88 CAG repeats. The most common natural occurring human allele encodes a stretch of 17 poly-glutamines.

Thus, one aspect of the present invention thus relates to a non-human animal model expressing at least one phenotype associated with DRPLA due to the introduction of at least one genetic determinant, wherein the at least one genetic determinant is a gene or DNA or fragment thereof, and/or RNA or fragment thereof and/or protein or part thereof of the human atrophin-1/cDNA, mRNA and/or protein (SEQ ID NO:52, SEQ ID NO:53), wherein the number of CAG repeats is at least 49, 55, 60, 70 or at least 80 repeats.

Similarly, one embodiment relates to the non-human animal model expressing at least one phenotype associated with DRPLA due to the introduction of at least one genetic determinant, wherein the at least one genetic determinant is a gene or DNA or fragment thereof, and/or RNA or fragment thereof and/or protein or part thereof of the porcine homolog of the human atrophin-1 gene/cDNA, mRNA and/or protein, wherein the number of CAG repeats is at least 49, 55, 60, 70 or at least 80 repeats.

The non-human animal model for DRPLA may be generated by introduction of said genetic determinant into a target cell by any method available to the skilled person, for example by injection into the target cell, or by virus-mediated transfer or any method suitable as known by the skilled person.

In one particular embodiment the non-human animal model for DRPLA is generated by sperm mediated gene transfer.

According to the present invention a pig model for DRPLA is in one embodiment produced by sperm mediated gene transfer of the human or the porcine homolog of the human atrophin-1 gene/cDNA, mRNA and/or protein, fragments or part thereof, wherein the number of CAG repeats is at least 49, 55, 60, 70 or at least 80 repeats.

However, the pig model for DRPLA may also be produced by introducing the human or porcine homolog of the human atrophin-1 gene/cDNA, mRNA and/or protein, fragments or part thereof, wherein the number of CAG repeats is at least 49, 55, 60, 70 or at least 80 repeats, or protein expressed thereof into a target cell.

The non-human animal model for DRPLA, in particular the pig model for ALS, will typically develop at least one of the symptoms epileptic seizures, myoclonus, ataxia, and dementia.

#### Spinal and Bulbar Muscular Atrophy (SBMA)

One embodiment of the present invention relates to a non-human animal model expressing at least one phenotype associated with SBMA. In a particular aspect the non-human animal model is a pig model expressing at least one phenotype associated with SBMA.

SBMA is caused by CAG repeat expansions in exon 1 of the androgen receptor (AR) gene on the X-chromosome results in spinal and bulbar muscular atrophy (Kennedy's disease) [37]. The normal length of the human CAG TNR is between 11 and 33 CAG copies and in diseased individuals the expansion ranges from 38 to 62.

Thus, one aspect of the present invention thus relates to a non-human animal model expressing at least one phenotype associated with SBMA due to the introduction of at least one genetic determinant, wherein the at least one genetic determinant is a gene or DNA or fragment thereof, and/or RNA or

fragment thereof and/or protein or part thereof of the human AR gene/cDNA, mRNA and/or protein (SEQ ID NO:54, SEQ ID NO:55), wherein the number of CAG repeats is at least 38, 45, 50, 55 or at least 60, or in the range of 38 to 62 repeats.

Similarly, one embodiment relates to the non-human animal model expressing at least one phenotype associated with SBMA due to the introduction of at least one genetic determinant, wherein the at least one genetic determinant is a gene or DNA or fragment thereof, and/or RNA or fragment thereof and/or protein or part thereof of the porcine homolog of the human AR gene/cDNA, mRNA and/or protein, wherein the number of CAG repeats is at least 38, 45, 50, 55 or at least 60, or in the range of 38 to 62 repeats.

The non-human animal model for SBMA may be generated by introduction of said genetic determinant into a target cell by any method available to the skilled person, for example by injection into the target cell, or by virus-mediated transfer or any method suitable as known by the skilled person.

In one particular embodiment the non-human animal model for SBMA is generated by sperm mediated gene transfer.

According to the present invention a pig model for SBMA is in one embodiment produced by sperm mediated gene transfer of the human or the porcine homolog of the human AR gene/cDNA, mRNA and/or protein, wherein the number of CAG repeats is at least 38, 45, 50, 55 or at least 60, or in the range of 38 to 62 repeats.

However, the pig model for SBMA may also be produced by introducing the human or porcine homolog of the human AR gene/cDNA, mRNA and/or, wherein the number of CAG repeats is at least 38, 45, 50, 55 or at least 60, or in the range of 38 to 62 repeats, or protein expressed thereof into a target cell.

The non-human animal model for SBMA, in particular the pig model for SBMA, will typically develop at least one of the symptoms: uncontrollable twitching (fasciculations) followed by weakness and wasting of the muscles becomes apparent sometime after the age of fifteen. The muscles of the face, lips, tongue, mouth, throat, vocal chords, trunk and limbs may be affected.

#### Huntington's Disease (HD)

One embodiment of the present invention relates to a non-human animal model expressing at least one phenotype associated with HD. In a particular aspect the non-human animal model is a pig model expressing at least one phenotype associated with HD.

"Huntington's disease" (also known as Huntington chorea) is used herein to refer to any inherited condition characterized by abnormal and/or uncontrolled body movements, mental and emotional problems, and loss of thinking ability (cognition).

Adult-onset Huntington disease, the most common form of this disorder, usually begins in middle age. Signs and symptoms can include irritability, depression, small involuntary movements, poor coordination, and trouble learning new information or making decisions. As the disease progresses, involuntary jerking movements (chorea) become more pronounced. Affected individuals may have trouble walking, speaking, and swallowing. People with the disorder also typically experience changes in personality and a decline in thinking and reasoning abilities. Individuals with this form of Huntington disease generally survive about 15 to 25 years after onset.

There is also an early-onset form of Huntington disease that begins in childhood or adolescence. Some of the clinical features of this disease differ from those of the adult-onset

form. Signs and symptoms can include slowness, clumsiness, rigidity, loss of developmental milestones (such as motor skills), slow speech, and drooling. Seizures occur in 30 percent to 50 percent of individuals with this condition. The course of early-onset Huntington disease may be shorter than adult-onset Huntington disease; affected individuals generally survive 10 to 15 years after onset.

Huntington's disease in humans is linked to the Huntingtin gene (HD gene, accession number: NM\_002111). The function of the corresponding protein is not yet known, but it likely plays an important role in nerve cells. The disease causing mutation in Huntington's disease is an extension of a CAG repeat, to a length above 35 CAG units. The number of repeats can to a certain extent be correlated with disease onset.

The expanded repeat leads to the production of a huntingtin protein that contains a long stretch of the amino acid glutamine. The elongated protein disrupts the normal function of nerve cells in certain parts of the brain, and ultimately leads to the death of those cells. The dysfunction and loss of nerve cells cause the signs and symptoms of Huntington disease.

Thus, one aspect of the present invention thus relates to a non-human animal model expressing at least one phenotype associated with HD due to the introduction of at least one genetic determinant, wherein the at least one genetic determinant is a gene or DNA or fragment thereof, and/or RNA or fragment thereof and/or protein or part thereof of the human Huntingtin gene/cDNA, mRNA and/or protein (SEQ ID NO:56, SEQ ID NO:57), wherein the number of CAG repeats is at least 35, 45, 50, 55 or at least 60.

Similarly, one embodiment relates to the non-human animal model expressing at least one phenotype associated with HD due to the introduction of at least one genetic determinant, wherein the at least one genetic determinant is a gene or DNA or fragment thereof, and/or RNA or fragment thereof and/or protein or part thereof of the porcine homolog of the human Huntingtin gene/cDNA, mRNA and/or protein, wherein the number of CAG repeats is at least 35, 45, 50, 55 or at least 60.

The non-human animal model for HD may be generated by introduction of said genetic determinant into a target cell by any method available to the skilled person, for example by injection into the target cell, or by virus-mediated transfer or any method suitable as known by the skilled person.

In one particular embodiment the non-human animal model for HD is generated by sperm mediated gene transfer.

According to the present invention a pig model for HD is in one embodiment produced by sperm mediated gene transfer of the human or the porcine homolog of the human Huntingtin gene/cDNA, mRNA and/or protein, wherein the number of CAG repeats is at least 35, 45, 50, 55 or at least 60.

However, the pig model for HD may also be produced by introducing the human or porcine homolog of the human huntingtin gene/cDNA, mRNA and/or, wherein the number of CAG repeats is at least 35, 45, 50, 55 or at least 60; or protein expressed thereof into a target cell.

The non-human animal model for HD, in particular the pig model for HD, will typically develop at least one of the symptoms described above such as slowness, clumsiness, rigidity, loss of developmental milestones (such as motor skills), slow speech, and drooling or seizures.

Dyschondroplasia (Collagen X Type)

In one embodiment of the present invention the non-human animal model expresses at least one phenotype associated with dyschondroplasia. In a particular aspect the non-human

animal model is a pig model expressing at least one phenotype associated with dyschondroplasia.

Chondrodysplasias are a group of disorders affecting the skeleton and are often associated with proteins of the collagen superfamily constituting at least 19 different types of collagen, these being major components of cartilages throughout the mammalian organism implicating roles in the processes of calcification and ossification [38]. One third of the collagens (types I, II, III, V, and IX) are denoted fibrillar collagens due to their tissual status as long, highly organised fibers. The remaining two thirds of the collagens are nonfibrillar and are further divided into two groups; the fibril associated with interrupted helices and the network forming collagens [39]. Collagen X belongs to the group of network forming collagens and has been reported to be expressed mainly in the hypertrophic region of growth plate cartilage [40], and has only rarely been detected in calcifying region of articular cartilage [41].

Type X collagen has been suggested to be structurally important in the extracellular matrix by offering the molecular milieu essential for endochondral bone formation [40]. Furthermore, it has been shown that type X collagen exists in osteochondrotic and osteoarthritic porcine articular cartilage and it may be a product of the cell population trying to repair the breakdown [41]. However, in osteochondrosis the endochondral ossification is impaired regardless of the unaltered collagen X levels in the growth plate and the increase of said collagen in articular cartilage. This could indicate that type X collagen alone is not able to cause ossification of cartilage [41]. Moreover, it has previously been shown, in a naturally occurring porcine model, that a mutation in the porcine non-collagenous domain 1 (NC1) of collagen X causes a phenotype similar to the human dwarfism Schmid metaphyseal chondrodysplasia (SCMD) [42]. Said cartilage disorder is an autosomal dominant disease which characteristics are short stature, coxa vara, and a waddling gait, and histopathological examinations show an extremely irregular organisation of the growth plate in long bones [43,44].

Transgenic animals are important tools as model organisms in basic research as well as in applied scientific areas and they have now been used for several years to study for instance gene function and human diseases. In relation to transgenesis, collagen X offers a unique opportunity regarding the detection of transgene expression, since wild type collagen X is almost selectively expressed in chondrocytes, making the detection of transgene expression in other tissues uncomplicated and hence easy to ascribe to the transgenic procedure.

One aspect of the present invention thus relates to a non-human animal model expressing at least one phenotype associated with dyschondroplasia due to the introduction of at least one genetic determinant, wherein the genetic determinant is a gene or DNA or fragment thereof, and/or RNA or fragment thereof and/or protein or part thereof of the human COL10A1 gene, mRNA and/or protein (SEQ ID NO:58, SEQ ID NO:59) being present in at least a transient manner.

Similarly, in one embodiment the non-human animal model expressing at least one phenotype associated with dyschondroplasia due to the introduction of a genetic determinant, wherein the genetic determinant is a gene or DNA or fragment thereof, and/or RNA or fragment thereof and/or protein or part thereof of the porcine COL10A1 gene, mRNA and/or protein corresponding to SEQ ID NO:60, SEQ ID NO:61 or fragments or parts thereof, being present in at least a transient manner.

The non-human animal model for dyschondroplasia may be generated by introduction of said genetic determinant into

a target cell by any method available to the skilled person, for example by injection into the target cell, or by virus-mediated transfer or any method suitable as known by the skilled person.

In one particular embodiment the non-human animal model for dyschondroplasia is generated by sperm mediated gene transfer.

According to the present invention a pig model for dyschondroplasia is in one embodiment produced by sperm mediated gene transfer of the constitutively expressed porcine COL10A1 of porcine or human origin as described elsewhere herein. However, the pig model for dyschondroplasia may also be produced by introducing the COL10A1 DNA or protein expressed thereof into a target cell.

The non-human animal model for dyschondroplasia, in particular the pig model for dyschondroplasia, will typically develop at least one of the symptoms described above such as disorders involving tubular bones, and characterized by a neoplasmlike proliferation of cartilage in the metaphyses that cause distorted growth in length or pathological fractures.

#### Non-Human Animals

The present invention relates to a non-human animal serving as a disease model for autosomal dominant disorders, for example neurodegenerative diseases such as protein conformation diseases such as listed elsewhere herein.

In one embodiment the non-human animal model may be any model with the proviso that the animal is not a rodent such as rat, mouse or hamster. The non-human animal is selected from the group consisting of ape, monkey, cattle, pig, sheep, goat, horse, donkey.

In a special embodiment of the present invention the non-human animal model is a pig.

In one embodiment the pig presenting the pig model is a wild pig. In another embodiment the pig is the domestic pig, *Sus scrofa*, such as *S. domesticus*. In yet another embodiment the invention relates to mini pigs, as well as to inbred pigs. The pig can be selected e.g. from the group consisting of Landrace, Yorkshire, Hampshire, Duroc, Chinese Meishan, Berkshire and Pietrain, such as the group consisting of Landrace, Yorkshire, Hampshire and Duroc, for example the group consisting of Landrace, Duroc and Chinese Meishan, such as the group consisting of Berkshire, Pietrain, Landrace and Chinese Meishan, for example the group consisting of Landrace and Chinese Meishan. In one embodiment, the pig is not a mini-pig.

In another embodiment of the present invention the pig is a mini-pig and the mini-pig is preferably selected from the group consisting of Goettingen, Yucatan, Bama Xiang Zhu, Wuzhishan and Xi Shuang Banna.

One aspect of the present invention relates to a non-human animal model produced by sperm-mediated gene transfer. The method of sperm mediated gene transfer of the present invention for the production of a non-human animal model for studying a hereditary autosomal dominant disease and/or for the production of a pig model for studying amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease, diseases associated with trinucleotide repeats, Huntington's chorea and/or dyschondroplasia comprises the steps of i) providing semen from a male, non-human animal ii) providing a genetic determinant capable of establishing said hereditary disease when the genetic determinant is expressed in said non-human animal model iii) contacting said semen and said genetic determinant iv) fertilising an oocyte from a female, non-human animal with the semen and the genetic determinant and v) incubating said fertilised oocyte under conditions allowing said fertilised oocyte to develop into said non-human animal model.

The semen for the method is provided from a male, non-human animal, in particular a boar. The selection of the sperm donor boars is crucial for the outcome of the procedure. The boars of choice are selected so that the initial sperm motility is >90%. Preferably the semen is fresh and collected in sterile 10 mL tubes and transported undiluted at a temperature not below 15° C. as this will cause damage to the sperm cells. The quality of the sperm cell and thus the efficiency of the sperm-mediated gene transfer procedure is affected by numerous factors such as season of year, collection frequency, breed and age of the donor. In order to choose the correct donor cells, the sperm cells from the different boars are examined under a light microscope. The sperm cells originating from the boar having the highest sperm cell motility after the washing procedure are chosen. Next, the sperm cells from the boar of choice are counted. It is important for the present invention that the sperm cell motility is maintained following the removal of seminal fluid.

In one embodiment the boar has abstained for 1 to 10 days, 2-8 days, 1-2 days or in a particular embodiment of the invention the donor boar has abstained for 2 days prior to collecting the semen to be employed in the procedure.

The mechanism of internalization of foreign DNA involves specific proteins capable of binding DNA in a CD4-like manner to sperm heads. The proteins of 30-35 kDa have been identified in a variety of species such as mice, cattle, pig and humans. However, under normal conditions the seminal fluid strongly protects the sperm cells from foreign DNA by antagonizing the binding of the DNA to be internalized. The main antagonist is inhibitory factor 1 (IF-1). Accordingly, the antagonist has to be removed or neutralised before the sperm is used in sperm-mediated gene transfer procedures. Therefore, in one embodiment of the present invention the seminal fluid is removed from the spermatozoa for example by washing.

Ejaculated spermatozoa will under normal conditions capacitate which means that the spermatozoa undergo physiological changes rendering the cells able to fertilise. Therefore, in one embodiment of the present invention the sperm-mediated gene transfer method the initiation of the sperm-DNA interaction should be started shortly after removal of the seminal fluid (for example during the washing step of the procedure). In another embodiment, in order to facilitate capacitation and correct sperm-DNA incubation time, the applied buffer is calcium free as calcium under normal conditions promotes capacitation. Additionally, the absence of calcium prevents endonucleases from acting on the foreign DNA. Thus, in a particular embodiment of the invention the sperm is washed in a buffer devoid of calcium. In a further particular embodiment the washing buffer comprises the following components are 56.1 g Glucose, 3.5 g EDTA (2H<sub>2</sub>O), 3.5 g Sodium citrate, 1.1 g Sodium bicarbonate (for 1 liter of buffer) dissolved in water and the solution is sterilized through a filter. Before the buffer is added to the sperm cells, 6 mg/ml BSA (Bovine Serum Albumine, Fraction V, Sigma) is added.

One preferred washing procedure according to the present invention is accomplished as fast as possible as follows: 5 mL sperm is transferred to a 50 mL tube and 5 mL washing buffer preheated to 37° C. is added, mix by inverting the tubes. The solution is incubated for 5 min at room temperature (approximately 22° C.) and 40 mL buffer (room temperature) is added. Upon centrifugation at 800 g, for 10 min at 25° C. the supernatant is removed and the pellet resuspended in 50 mL buffer (room temperature). The mixture is subjected to centrifuga-

tion at 800 g, for 10 min at 17° C. and the supernatant is removed. The pellet is carefully resuspended in the remaining buffer in the tube.

When the genetic determinant has been provided the semen is contacted with the genetic determinant. Sperm cells are diluted in buffer as described above for the washing of sperm cells. In one embodiment the buffer temperature is in the range of 15° C. to 25° C., and in particular the temperature is 17° C. The genetic determinant in the form of DNA is added to the diluted sperm cells. The concentration of the genetic determinant is in the range of 0.1 µg to 1 µg per 10<sup>6</sup> sperm cells. In a particular embodiment the genetic determinant is linearised DNA added in a concentration of 0.4 µg linearised DNA/10<sup>6</sup> sperm cells.

In one particular embodiment the following procedure is used:

10<sup>9</sup> sperm cells are diluted into 120 mL 17° C. buffer  
0.4 µg linearised DNA/10<sup>6</sup> sperm cells is added (that is, a total of 400 µg linearised DNA)

Incubate 100 min at 17° C.

To avoid sedimentation of the cells, invert the tube every 20 min

Transfer the tube to room temperature, and transport it (at room temperature) to animal houses or stable facilities (approx. 10 minutes.)

The incubated sperm cells are now ready to be applied in artificial insemination methods.

The non-human animal model and in particular the pig models of the present invention may be produced by methods other than sperm mediated gene transfer, for example by pronuclear microinjection, somatic cell nuclear transfer, or retrovirus mediated gene transfer.

A further aspect of the present invention pertains to a non-human sperm cell comprising at least one genetic determinant exerting at least one dominant phenotype for at least one hereditary disease when expressed in a non-human animal host organism. The non-human sperm cell may originate from any of the animals listed elsewhere herein. As described in detail elsewhere herein the genetic determinant is of mammalian origin, for example of human and/or porcine origin. The non-human sperm cell may be a non-human sperm cell exerting an autosomal dominant phenotype for a hereditary disease such as any of the diseases according to the present invention. The non-human host organism is any of the animals presented herein, and in particular a pig.

The non-human sperm cell according to the present invention may be produced by a method comprising the steps of a) providing a non-human sperm cell, b) providing at least one genetic determinant exerting a dominant phenotype for a hereditary disease when expressed in a non-human animal host organism, c) contacting said non-human sperm cell and said at least one genetic determinant, wherein said contacting results in the uptake of the genetic determinant into the non-human sperm cell.

A further aspect of the invention relates to a composition comprising a non-human sperm cell in combination with at least one genetic determinant exerting at least one dominant phenotype for at least one hereditary disease when expressed in a non-human animal host organism. In preferred embodiments the genetic determinant is of human and/or porcine origin.

The present invention also discloses a method for fertilising an oocyte by sperm-mediated gene transfer. The method comprises the steps of providing the non-human sperm cell as carrying the at least one genetic determinant for a phenotype associated with autosomal dominant diseases as defined herein and introducing the non-human sperm cell into the

oocyte to be fertilised. Consequently, another aspect of the invention relates to a method for fertilising an oocyte by sperm-mediated gene transfer, wherein the method comprises the steps of providing the composition as described herein and introducing the composition into the oocyte to be fertilised.

Therefore, the present invention also pertains to an embryo obtained by fertilising an oocyte with the non-human sperm cell comprising at least one genetic determinant exerting at least one dominant phenotype for at least one hereditary disease of the present invention when expressed in a non-human animal host organism. Similarly an embryo obtained by fertilising an oocyte with the composition as disclosed herein is within the scope of the present invention. Furthermore, as an embryo has been established the present invention offers a method for the cultivation and development of the embryo comprising the step of cultivating the embryo under conditions allowing the embryo to develop into a non-human animal offspring expressing said genetic determinant and exerting a dominant phenotype for a hereditary disease.

The presence of a non-human animal model of autosomal dominant diseases provides the opportunity of evaluating whether a given pharmaceutical composition, compound, treatment and/or drug has an effect on the phenotype of the given non-human animal. Therefore, it is within the scope of the present invention to provide for a method for evaluating the response of a therapeutical treatment of a hereditary disease, said method comprising the steps of a) providing the non-human animal model according to the invention b) treating said non-human animal with at least one pharmaceutical composition exerting an effect on said at least one phenotype, and c) evaluating the effect observed. Additionally, the method also allows for a further step of advising on medical treatment of for example a human being suffering from an autosomal dominant disease such as a neurodegenerative diseases, protein conformation diseases such as ALS, Alzheimer's disease, HD, PD, trinucleotide repeat-associated diseases but also dyschondroplasia based on the effects observed during the method of evaluation.

In addition the availability of a non-human animal model expressing a particular phenotype associated with autosomal dominant diseases offers the ability of providing a method for screening the efficacy of a pharmaceutical composition, wherein the method comprises the steps of a) providing the non-human animal model of the present invention, b) expressing in said animal model said at least one genetic determinant and exerting said dominant phenotype for said hereditary disease, c) administering to said non-human animal the pharmaceutical composition the efficacy of which is to be evaluated, and d) evaluating the effect, if any, of the pharmaceutical composition on the phenotype exerted by the genetic determinant when expressed in the non-human animal model.

Furthermore, the present invention also relates to a method for treatment of a human being suffering from an autosomal dominant disease, wherein the method comprises the initial steps of a) providing the non-human animal model of the present invention, b) expressing in said animal model said genetic determinant and exerting said dominant phenotype for said hereditary disease, c) treating said non-human animal with a pharmaceutical composition exerting an effect on said phenotype, d) evaluating the effect observed, and e) treating said human being suffering from said hereditary disease based on the effects observed in the non-human animal model.

Moreover, a method for linking a genetic determinant with the occurrence of a hereditary disease in a human being is also

disclosed, said method comprising the steps of a) cultivating and developing an embryo obtained by fertilising an oocyte with a non-human sperm cell and a genetic determinant potentially constituting an autosomal dominant disease gene, for example a porcine gene exerting a dominant phenotype for a disease, such as a neurodegenerative disease when expressed in a non-human animal host organism, wherein said cultivation and development result in the generation of a non-human animal offspring, and b) observing whether said genetic determinant confers said autosomal dominant disease in said non-human animal offspring.

## EXAMPLES

### Example 1

#### Transgenic Porcine Model of Amyotrophic Lateral Sclerosis (ALS)

In order to establish transgenic pigs which could serve as potential animal models for the human neurodegenerative disease ALS, a mutation, Gly93Arg, was introduced into the gene encoding porcine SOD1 by means of site directed mutagenesis. The choice of mutation was based on protein structural speculations, since the crystal structure of human SOD1 reveals an extremely condensed structure, showing that a substitution of the small relatively flexible glycine at position with the large charged arginine is likely to cause severe alteration in the protein. Furthermore, several different substitutions at this position cause ALS in humans including the G93R mutation [45,46]. In order to impede possible truncation of important elements in the DNA construct following the SMT procedure the DNA fragment containing the porcine SOD1 cDNA contains additional nucleotides 5'- and 3'-prime to the CMV promoter and SVpolyA fragment. Totally, as shown in FIG. 1, the fragment used to make transgenic animals constitutes approximately 2100 bp.

#### RNA Isolation and cDNA Synthesis

Various porcine tissues were dissected from slaughtered pigs (Duroc boars and Landrace-Yorkshire sows (DxLY) and immediately frozen in liquid nitrogen and stored at -80° C. 100 mg of the tissue of choice was used for RNA isolation. RNA was isolated using the Nucleospin, Midi Kit from Macherey-Nagel.

cDNA synthesis was accomplished by mixing 1 µg of total RNA with 1 µL of oligo (dT) 12-18 (500 µg/mL), and DEPC treated H<sub>2</sub>O to a final volume of 12 µL. The mixture was incubated at 70° C. for 10 min, after which 4 µL of 5× first-strand buffer, 2 µL of 0.1 mM DTT, 1 µL of 10 mM dNTP mix and 1 µL (200 U/µL) of Superscript II (Invitrogen) was added and the sample was further incubated at 42° C. for 1 hour followed by an inactivation step at 70° C. for 15 min. Sequencing Genes of Interest, Including Porcine SOD1

Based on homology search between the human SOD1 gene and an "in house" porcine EST database, 2 primers (SOD1\_CDF and SOD1\_CDR) were designed for amplification of the cDNA for the porcine SOD1 gene. The PCR reaction was performed in a total volume of 25 µL consisting of 2.5 µL of 10× reaction buffer, 4 µL of dNTP (2.5 mM), 1 µL of both forward and reverse primer (10 pmol each), 1 µL 1 U/µL Dynazyme polymerase (Finnzymes), 2 µL cDNA template, and 13.5 µL H<sub>2</sub>O.

The touchdown PCR reaction was performed in a GeneAmp® PCR System 9700 (Applied Biosystems) under the following conditions: Initial denaturation at 95° C. for 3 min, denaturation at 95° C. for 30 sec, touchdown from 63° C. to 58° C. with a decrement of 0.5° C. for 30° C., followed by 1

min of elongation at 72° C. per cycle. Furthermore 35 cycles of 30 sec denaturation at 95° C., 30 sec of annealing at 58° C., and 1 min of elongation at 72° C. was included together with a final elongation step at 72° C. for 7 min.

The primers used to amplify the SOD1 cDNA were:

(SEQ ID NO: 62)  
SOD1\_CDF: 5' -ATGGCGACGAAGGCCGTGT-3'

(SEQ ID NO: 63)  
SOD1\_CDR: 5' -TTACTGGGTGATCCCAATTACACCAC-3'

The PCR product was purified using QIAEX® II Gel Extraction Kit (Qiagen) from a 1% Seakem agarose gel.

Amplicons were cloned into the pCR®2.1-TOPO vector (Invitrogen, CA) using manufactures recommendations and, applying standard procedures, clones were subsequently sequenced to ensure that they contained the SOD1 amplicon.

The porcine SOD1 cDNA sequence is shown in FIG. 1

Cycle sequencing reactions were accomplished in a GeneAmp® PCR System 9700 (Applied Biosystems) where an initial denaturation step at 95° C. for 2 min, 99 cycles of 10 sec denaturation and 4 min elongation at 60° C., was applied to the sample mixture consisting of: 1.5 µL of Big Dye Terminator mix version 3.1, 1 µL of primer (5 pmol), 2 µL of a 5× reaction buffer, 2 µL of the purified PCR product and 3.5 µL H<sub>2</sub>O. Sequencing product were precipitated with 2.5 volumes of ethanol and 1/10 volume of 3 M NaAc, air dried and resuspended in 10 µL formamide (sequencing grade). The samples were run on a 3730xl DNA Analyzer (Applied Biosystems). Site Directed Mutagenesis of Porcine SOD1

In order to introduce the Gly93Arg mutation into SOD1 site directed mutagenesis was performed using the QuickChange® XL Site-Directed Mutagenesis Kit (Stratagene) and accomplished in accordance with the manufacturer's recommendations as described herein. The PCR reaction was performed in a total volume of 50 µL consisting of 5 µL of 10× reaction buffer, 2 µL of both forward and reverse primer (10 pmol each), 1 µL dNTP mix, 3 µL QuickSolution, 1 µL PfuTurbo® DNA polymerase (2.5 U/µL), 1 µL TOPO-SOD1 template (10 ng), and 35 µL H<sub>2</sub>O.

Forward and reverse primers used for the above PCR procedure were:

SOD1G93R\_F: (SEQ ID NO: 64)  
5' -GACTGCTGGCAAAGATCGTGTGGCCACTGTGTATAC-3'

SOD1G93R\_R: (SEQ ID NO: 65)  
5' -GATGTACACAGTGGCCACACGATCTTTGCCAGCAGTC-3'

The PCR reaction was accomplished in a GeneAmp® PCR System 9700 (Applied Biosystems) under the following conditions: Initial denaturation at 95° C. for 1 min, 18 cycles of 50 sec denaturation at 95° C., 50 sec of annealing at 60° C., and 6 min of elongation at 68° C. and a final elongation step at 68° C. for 7 min.

Subsequently 1 µL of Dpn I (10 U/µL) was added to the sample mixture in order to digest the nonmutated parental DNA template. The reaction was incubated for 1 hour at 37° C. After digestion of the parental DNA template XL10-Gold® Ultracompetent Cells (Invitrogen, CA) were transformed with the Dpn I treated DNA in the following manner: XL10-Gold® Ultracompetent Cells were thawed on ice and 45 µL were aliquoted to a prechilled Eppendorf tube and 2 µL of β-mercaptoethanol was added followed by a gentle swirling of the tube. The tube was now left on ice for 10 min. After

incubation, 2  $\mu$ L of the Dpn I treated DNA was added, the sample was swirled and incubated on ice for another 30 min and then exposed to a heat pulse of 42° C. for 30 sec. Subsequently, the sample was put on ice for 2 min followed by an addition of 0.5 mL 42° C. NZY+broth. The mix was plated onto LB-amp plates and incubated overnight at 37° C. To ensure that the mutation of interest was integrated in the porcine SOD1 gene, 16 colonies were picked and grown overnight in liquid LB-Amp media and plasmids were purified using the QIAprep® Spin Miniprep kit (Qiagen) according to manufactures recommendations. Cycle sequencing reactions were accomplished in a GeneAmp® PCR System 9700 (Applied Biosystems) where an initial denaturation step at 95° C. for 2 min, 99 cycles of 10 sec denaturation and 4 min elongation at 60° C., was applied to the sample mixture consisting of: 1.5  $\mu$ L of Big Dye Terminator mix version 3.1, 1  $\mu$ L of either T7 or SP6 primer (5 pmol), 2  $\mu$ L of a 5 $\times$  reaction buffer, 1  $\mu$ L of the purified plasmid and 4.5  $\mu$ L H<sub>2</sub>O. Sequencing product were precipitated with 2.5 volumes of ethanol and 1/10 volume of 3 M NaAc, air dried and resuspended in 10  $\mu$ L formamide (sequencing grade). The samples were run on a 3730xl DNA Analyzer (Applied Biosystems). Sequences were checked and a plasmid containing the mutation was chosen as template for the subsequent procedures. The sequence of the mutated porcine SOD1 cDNA is shown in FIG. 2.

#### Cloning of Gene(s) of Interest—SOD1 into the Expression Vector, pHCMV1

To facilitate a continuous high expression of the transgene of interest, the gene was cloned into the pHCMV1 vector (Gene Therapy Systems). For release of the mutated SOD1 DNA 6  $\mu$ L plasmid DNA was digested with 1.5  $\mu$ L EcoRI (20 U/ $\mu$ L) in a total volume of 30  $\mu$ L in addition of 3  $\mu$ L EcoRI 10 $\times$  reaction buffer. The reaction was incubated at 37° C. for 90 min and run on a 1% Seakem GTG agarose gel. The correctly sized band was isolated from the agarose gel employing a QIAEX® II Gel Extraction Kit (Qiagen) and dissolved in 30  $\mu$ L H<sub>2</sub>O. Likewise, pHCMV1 was EcoRI digested and isolated from a 0.8% Seakem GTG agarose gel and dissolved in 30  $\mu$ L H<sub>2</sub>O. Furthermore, in order to avoid self-ligation of the vector, 6  $\mu$ L of the digested pHCMV1 vector was dephosphorylated in a total volume of 25  $\mu$ L applying 1.5  $\mu$ L CIP (10 U/ $\mu$ L) and 2.5  $\mu$ L 10 $\times$ CIP reaction buffer. The sample was incubated 60 min at 37° C. Enzyme inactivation occurred at 80° C. for 15 min.

Ligation of mutagenised SOD1 into the EcoRI digested and dephosphorylated pHCMV1 was performed in a total volume of 15  $\mu$ L in the addition of 3  $\mu$ L dephosphorylated pHCMV1, 8  $\mu$ L EcoRI linked mutagenised SOD1, 1.5  $\mu$ L T4 DNA ligase (400 U/ $\mu$ L), 1.5  $\mu$ L 10 $\times$ T4 DNA ligase buffer, and 1  $\mu$ L H<sub>2</sub>O. The reaction was incubated at 16° C. overnight. XL10-Gold® Ultracompetent Cells were thawed on ice and 45  $\mu$ L were aliquoted to a prechilled ependorf tube and 2  $\mu$ L of  $\beta$ -mercaptoethanol was added followed by a gentle swirling of the tube. The sample was now left on ice for 10 min. After incubation, 3  $\mu$ L of the ligation mix was added, the sample was swirled and incubated on ice for another 30 min and then exposed to a heat pulse of 42° C. for 30 sec. Subsequently, the sample was put on ice for 2 min followed by an addition of 0.5 mL 42° C. NZY+broth. The mix was plated onto LB-amp plates and incubated overnight at 37° C.

To ensure that the insert had integrated correctly into the pHCMV1 vector 16 colonies were picked and grown overnight in liquid LB-Amp media and plasmids were purified using the QIAprep® Spin Miniprep kit (Qiagen) in accordance with manufactures recommendations. Cycle sequencing reactions were accomplished in a GeneAmp® PCR Sys-

tem 9700 (Applied Biosystems) where an initial denaturation step at 95° C. for 2 min, 99 cycles of 10 sec denaturation and 4 min elongation at 60° C., was applied to the sample mixture consisting of: 1.5  $\mu$ L of Big Dye Terminator mix version 3.1, 1  $\mu$ L of either T7 or SP6 primer (5 pmol), 2  $\mu$ L of a 5 $\times$  reaction buffer, 1  $\mu$ L of the purified plasmid and 4.5  $\mu$ L H<sub>2</sub>O. Sequencing product was precipitated with 2.5 volumes of ethanol and 1/10 volume of 3 M NaAc, air dried and resuspended in 10  $\mu$ L formamide (sequencing grade). The samples were run on a 3730xl DNA Analyzer (Applied Biosystems). Sequences were checked and a plasmid containing the SOD1 construct in the correct direction was chosen.

#### Large Scale Preparation of DNA

In order to create DNA for incubation of sperm cells both PCR and large scale plasmid preparations have been employed.

The PCR reaction was performed in a GeneAmp® PCR System 9700 (Applied Biosystems) in a final volume of 25  $\mu$ L consisting of 5  $\mu$ L 5 $\times$  Phusion HF buffer, 2  $\mu$ L dNTP (2.5 mM each) 0.63  $\mu$ L forward and reverse primer 5 pmol, 0.1  $\mu$ L Phusion DNA Polymerase (2 U/ $\mu$ L), 1  $\mu$ L SOD1-pHCMV1 template, and 15.6  $\mu$ L H<sub>2</sub>O. The PCR reaction consisted of an initial denaturation at 98° C. for 30 sec followed by 30 cycles of denaturation for 10 sec at 98° C., annealing at 74° C. for 30 sec and elongation for 95 sec at 72° C. followed by a final elongation step at 72° C. for 7 min.

The following primers were used to amplify the mutagenised SOD1 construct plus the flanking (for var termen matching) CMV promoter, intron sequence, and SVpolyA, generating a fragment of 1643 bp+the mutagenised SOD1 fragment, generating a fragment of approximately 2100 bp:

(SEQ ID NO: 66)  
pHCMVF: 5' -GTCGGAACAGGAGAGCGCACGAGGG-3'

(SEQ ID NO: 67)  
pHCMVR: 5' -GGGTGATGGTTCACGTAGTGGGC-3'

In order to purify the generated PCR product a "High Pure PCR Product Purification Kit" (Roche) was applied. The suppliers' instructions were followed throughout the purification procedure. The PCR purified fragments were sequenced to check for errors in the sequence as described below.

Large scale plasmid preparation was accomplished from 1/2 liter *E. coli* cell cultures. Purification of plasmids was performed using a Plasmid Mega Kit (Qiagen). In order to linearise and release the desired fragment from the vector, the vector was digested with BssS I and Dra III in the following way: 1.5  $\mu$ L BssSI (4 U/ $\mu$ L), 1.5  $\mu$ L DraIII (20 U/ $\mu$ L), 3  $\mu$ L 10 $\times$ BSA, 3  $\mu$ L 10 $\times$ Ne buffer 3, and 2  $\mu$ L plasmid DNA was added to 19  $\mu$ L H<sub>2</sub>O to yield a total volume of 30  $\mu$ L and was left overnight at 37° C. The digested fragments were separated on a 0.8% GTG Seakem agarose gel and the correctly sized band were isolated and extracted from the gel using QIAquick Gel Extraction Kit Protocol (Qiagen), according to manufactures recommendations.

Both the PCR purified fragments and the plasmid prepared fragments were sequenced to check for errors in the sequence. Cycle sequencing reactions were accomplished in a GeneAmp® PCR System 9700 (Applied Biosystems) where an initial denaturation step at 95° C. for 2 min, 99 cycles of 10 sec denaturation and 4 min elongation at 60° C., was applied to the sample mixture consisting of: 1.5  $\mu$ L of Big Dye Terminator mix version 3.1, 1  $\mu$ L of either T7 or SP6 primer (5 pmol), 2  $\mu$ L of a 5 $\times$  reaction buffer, 1  $\mu$ L of the purified plasmid and 4.5  $\mu$ L H<sub>2</sub>O. Sequencing product were precipi-

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tated with 2.5 volumes of ethanol and  $\frac{1}{10}$  volume of 3 M NaAc, air dried and resuspended in 10  $\mu$ L formamide (sequencing grade). The samples were run on a 3730xl DNA Analyzer (Applied Biosystems).

FIG. 3 illustrates a comparison of the deduced amino acid sequence of porcine SOD1 with human, mouse and rat. The amino acid (G) which is mutated is marked in bold.

FIG. 4 shows projection of mutations in SOD1 onto the crystal structure of the human SOD1 dimer. The mutations are distributed all over the protein, illustrating that all residues of the protein are important for correct function of the enzyme.

#### Preparation of Sperm and DNA Uptake

##### Selection of Sperm Donor Boars

The selection of the sperm donor boars are crucial for the outcome of the procedure. A boar station (Hatting KS Viborg), have therefore been contacted and the boars of choice are selected so that the initial sperm motility is >90%. The sperm is collected in sterile 10 mL tubes and transported undiluted at a temperature not below 15° C. as this will cause damage to the sperm cells.

First and second semen ejaculate, were collected from 8 different boars yielding 16 semen fractions in total. All fractions of spermatozoa had an initial motility of 90 prior to the washing procedure. Seminal fluid was quickly removed by centrifugation and washing the sperm in Fertilization Buffer (FB) consisting of 56.1 g Glucose, 3.5 g EDTA (2H<sub>2</sub>O), 3.5 g Sodium Citrate (2H<sub>2</sub>O), and 1.1 g sodium bicarbonate dissolved in 1 liter of sterilized water. Furthermore 6 mg/ml BSA (Fraction V, Sigma) was added. Briefly, 5 mL of FB/BSA prewarmed to 37° C. was added to 5 mL of undiluted semen, mixed by inverting the tube, and left for 5 minutes at room temperature (approximately 22° C.). Next, FB/BSA at room temperature was added to 50 mL and centrifuged for 10 minutes at room temperature at 500 g, or alternatively at 800 g for 10 min at 25° C. The supernatant was removed and semen was resuspended in 50 mL FB/BSA at room temperature and further centrifuged at 500 g at 17° C., after which, the supernatant was removed again and the spermatozoa was resuspended in 15 mL of FB/BSA. Next, in order to choose the optimal donor cells, the spermatozoa from the different boars and the two separate ejaculates were quickly examined under a light microscope. The sperm cells originating from the two boars having the highest sperm cell motility after the washing procedure were chosen as vehicles for the subsequent transgenic procedures. Furthermore, the spermatozoa were counted.

##### Generation of Transgene Pigs

$1 \times 10^9$  sperm cells washed spermatozoa from each of the two chosen donor boars were incubated for 100 minutes at 17° C. with the linearized SOD1 DNA fragment (FIG. 5) in a concentration of 0.4  $\mu$ g DNA/106 spermatozoa in a suspension of 120 mL FB/BSA. Containers were inverted every 20 minutes to prevent sedimentation of spermatozoa. Finally, the mixture was incubated 10 minutes at room temperature and employed in artificial insemination of two sows in natural heat.

##### Animals

Two recipient sows (Danish Landrace $\times$ Yorkshire) at approximately 140 kg were selected due to their natural heating period and used for artificial insemination ( $1 \times 10^9$  DNA treated sperm (spermatozoa)/sow) meeting standard insemination procedures. Insemination was accomplished in the local stable areas at DIAS. Semen was collected from trained Danish Landrace boars that have abstained for 2 days. Semen was treated according to aforementioned procedures. Both sows were examined for pregnancy 24 and 42 days after

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insemination, showing that only one of the sows was pregnant. After ended gestation period, 2 boars and 5 sow piglets were born naturally. Animal care and experimental procedures met local, national and European Union Guidelines.

##### Analysis of Piglets

##### Test for the Transgene

After 115 days (20 Jun. 2005) 7 normal looking piglets were born, 2 of these were boar piglets and 5 were sow piglets. Blood samples were collected from the piglets in 6 mL EDTA blood collection tubes. Furthermore, blood from a wild type animal was collected as well and handled together with the 7 aforementioned animals. DNA was purified according to standard blood purification procedures in special clean laboratories, in order to avoid any possible contamination.

The PCR reaction was performed in a total volume of 10  $\mu$ L consisting of 1  $\mu$ L 10 $\times$ MgCl<sub>2</sub> free reaction buffer, 0.4  $\mu$ L 50 mM MgCl<sub>2</sub>, 1  $\mu$ L of both forward and reverse primer (10 pmol each), 0.5  $\mu$ L dNTP mix, 0.5  $\mu$ L DyNazyme EXT DNA polymerase (1 U/ $\mu$ L), 0.5  $\mu$ L DNA template (50 ng), and 5.1  $\mu$ L H<sub>2</sub>O.

Forward and reverse primer used for the above PCR procedure:

(SEQ ID NO: 68)  
PhCMV\_430F: 5'-GTCTCCACCCCATGACGTC-3'

(SEQ ID NO: 69)  
PhCMV\_646R: 5'-GGATCGGTCCCGGTGTCCTC-3'

The touchdown PCR reaction was accomplished in a GeneAmp® PCR System 9700 (Applied Biosystems) under the following conditions: Initial denaturation at 95° C. for 3 min, denaturation at 95° C. for 30 sec, touchdown from 62° C. to 57° C. with a decrement of 0.5° C. for 20 sec, followed by 1 min of elongation at 72° C. per cycle. Furthermore 35 cycles of 30 sec denaturation at 95° C., 20 sec of annealing at 57° C., and 1 min of elongation at 72° C. was included together with a final elongation step at 72° C. for 7 min.

This created PCR fragments of 218 bp and the result is shown in FIG. 6.

FIG. 6 shows that all animals (4905-4911) are positive regarding the transgenic DNA fragment. However, mosaicism can not be ruled out neither the possibility of the various animals having different copy numbers. Therefore 2 animals were sacrificed (pig 4906 and pig 4909) and various tissues were sampled and snap frozen in liquid nitrogen and subsequently stored at -80° C. DNA was purified from the different tissues and the same PCR as above was performed, the only difference being that the amount of DNA was not normalized.

The result of the PCR for animal 4906 and 4909 is shown in FIGS. 7 and 8, respectively.

FIGS. 7 and 8 show that nearly all tissues applied in the PCR control harbor the transgenic fragment. Furthermore, it should be noted that the genomic template DNA is not normalized regarding concentration. Still, the lack of DNA fragments in lane 9 in FIG. 6 and in lanes 3 and 5 in FIG. 8 could well be explained by a mosaic nature of the animals regarding the transgene. However, for pigs 4906 and 4909 the transgene is present in a large variety of tissues.

##### Transgene in the Germ Cells

In order to transfer the transgene to next generation it is important to ensure that the transgene is present in the germ cells. Therefore, DNA has been extracted from sperm cells from the two boars (4905 and 4908). The purification of DNA

was accomplished using two different procedures, standard purification procedure and miniprep purification procedure: Standard Purification Procedure

300  $\mu$ L of semen was washed in 1 mL 0.9% NaCl, followed by centrifugation for 5 min at 3000 rpm where after the supernatant was discarded. This step was repeated twice and 20  $\mu$ L Pronase (20 mg/mL), 20  $\mu$ L 1 M DTT, and 300  $\mu$ L buffer S was added to each sample, where after these were left to incubate at room temperature overnight. Subsequently, 180  $\mu$ L 6 M NaCl was added to each sample and shaken vigorously for approximately 20 seconds. The samples were now centrifuged for 15 min. at 10000 rpm and the supernatant was then carefully transferred to a new eppendorf tube where the DNA was precipitated adding twice the volume of supernatant and centrifuged at 10000 rpm for 10 min. Subsequently the ethanol was removed and the DNA was air dried and resuspended in 300  $\mu$ L of nuclease free water.

#### Miniprep Purification Procedure

300  $\mu$ L of semen was washed in 1 mL 0.9% NaCl, followed by centrifugation for 5 min at 3000 rpm where after the supernatant was discarded. This step was repeated twice and 20  $\mu$ L Pronase (20 mg/mL), 20  $\mu$ L 1 M DTT, and 300  $\mu$ L buffer S was added to each sample, where after these were left to incubate at room temperature overnight. In order to enrich each sample regarding low molecular DNA and obtain a more pure DNA product the miniprep procedure from Qiagen was applied. The DNA was eluted in 200  $\mu$ L of nuclease free water.

Buffer S composition: 10 mM Tris HCl (pH 8.0); 100 mM NaCl; 10 mM EDTA (pH 8.0); 0.5% SDS; H<sub>2</sub>O.

DNA from both procedures was employed in the same PCR test as already mentioned and the result is shown in FIG. 9.

FIG. 9 shows that the transgene is present in the sperm cells, however DNA purified with the miniprep purification procedure clearly shows much more distinct bands than the DNA purified with the standard procedure. This is probably due either the DNA being more pure or to the DNA being present as extra chromosomal fragments. Still, as the two boars harbor the transgene, these will be used in the production of the next transgene SOD1 generation.

#### Veterinary Declaration

Extracts from Veterinary Declarations dated 9th of Feb. 2006 and 9th of Mar. 2006, respectively, concerning transgenic animals are disclosed below.

"The boar 4905 has a bent back and very straight hocks. It raises and lays down with difficulty and stands with uneasiness in the back portion, seems slightly ataxic. A significant deterioration has occurred as compared to last month. No direct signs of soreness in the limbs.

It is unclear if the cause is in the big joints at the back and pelvis region or the nerve system. Neurological symptoms of ataxia in the back portion of pigs are normally assumed to be caused by damages in the bone marrow and not the brain. Ataxia can be due to a lacking proprioception, i.e. feeling of the positioning of the limbs.

The remaining pigs in the experiment move freely around."

The above section is a translation of an extract of a Veterinary Declaration dated 9th of Feb. 2006.

"White 4905: Boar in normal condition and without signs of external damages. It stands on both front and rear legs, but is a little insecure when having to move and if pushed. This is clear from slight ataxic movements: Crosses front legs and have cocked angles from time to time and stands with rear legs widely to the side. Strong itching reflex can be released by touching the backside. Eats and drinks normally. No signs of limping.

White 4908: Boar in normal condition and without signs of external damages. It stands with underpositioned ("under-stilled") rear legs. It is slightly ataxic when turning and pushes from the side. No signs of limping.

White 4907, 4911, 4910: 3 sows move freely. They show some signs of slight ataxic movements which can be provoked when pushing them around."

The above section is a translation of an extract of a Veterinary Declaration dated 9th of Mar. 2006.

#### Analysis of Transgenic Piglets

##### Biological Samples

Blood samples were withdrawn 3 days after birth and when the piglets reached 115 days blood samples were withdrawn every third week in 6 mL EDTA tubes and 6 mL serum tubes.

Two sows were sacrificed at the age of 5 month, and before any phenotypic changes could be observed. One 1 boar, 4908 was sacrificed at the age of 14 month and another boar, 4905, was sacrificed at the age of 15 month. Both boars had severe phenotypic changes. For all sacrificed animals various tissues have been snap frozen in liquid nitrogen and subsequently stored at -80° C. Furthermore, various tissues, including porcine brains have been fixed in formalin.

##### DNA and RNA Studies of Transgenic Pigs

DNA was prepared from EDTA stabilized blood samples and from snap frozen tails.

RNA was prepared from snap frozen tissues from heart, kidney, liver, lung, spleen, medulla spinalis (M. spinalis), frontal cortex (FCO), parietal cortex (PCO), musculus longissimus dorsi (M. L. dorsi), musculus semitendinosus, left side (M.semit. l.), musculus semitendinosus, right side (M.semit. r.), musculus semibranosus, left side (M.semb. l.), and musculus semibranosus. All DNA and RNA samples were extracted in special clean laboratory facilities under highly stringent experimental conditions using standard protocols.

##### PCR Evaluation

50 ng of genomic DNA isolated from blood samples from each of the seven pigs were amplified using the following primers: SOD1 Exon3F: 5'-GCTGTACCAGTGCAGGTC-CTC-3' (SEQ ID NO:70) and SOD1 Exon4R: 5'-CCATTGTGCGGCCAATGATG-3' (SEQ ID NO:71) yielding a fragment of approximately 800 bp when amplifying the endogenous genomic SOD1 and approximately 200 bp when amplifying the exon 3 to exon 4 cDNA fragment. The following sample mix was employed 1  $\mu$ L 10 $\times$ MgCl<sub>2</sub> free reaction buffer, 0.4  $\mu$ L 50 mM MgCl<sub>2</sub>, 10 pmol of each primer, 5 mM dNTP-mix, and 0.5 U Dynazyme Ext DNA polymerase. The reaction was performed in a total volume of 10  $\mu$ L and accomplished as a touchdown PCR in a GeneAmp® PCR system 9700 (Applied Biosystems) under the following conditions: Initial denaturation at 95° C. for 3 min, denaturation at 95° C. for 30 sec, touchdown from 62° C. to 57° C. with a decrement of 0.5° C. for sec, followed by 1 min of elongation at 72° C. per cycle. Furthermore, 35 cycles of 30 sec denaturation at 95° C., 20 sec of annealing at 57° C., and 1 min of elongation at 72° C. was included together with a final elongation step at 72° C. for 7 min.

##### Expression Analysis

Of the total RNA, 2  $\mu$ g was reverse transcribed from the various tissues, employing a SuperScript III kit (Invitrogen, USA) according to manufactures recommendation using random hexamer primers. RT-PCR experiments were conducted in triplicate. The risk of amplifying genomic DNA was apart from primer designed to span exon-exon junctions ruled out by running the PCR prior to reverse transcription. Quantitative real time PCR was performed using the TaqMan® assay and PCR amplification in an ABI-PE prism 7900 sequence detection system (PE Applied Biosystems). Primers,

ssSOD1\_EX4F 5'-GGATCAAGAGAGGCACGTTGG-3' (SEQ ID NO:72) and ssSOD1\_EX4R 5'-GGCGATCACA-GAATCTTCGATG-3' (SEQ ID NO:73), and MGB probes were designed using the Primer Express Software 2.0 (PE Applied Biosystems), and the MGB probes, designed to match the endogenous and mutated porcine SOD1, were designed with VIC and FAM as reporter dyes (SS\_SOD1\_WT: VIC-5'-CAAAGATGGTGTGGCCAC-3' (SEQ ID NO:74) and SS\_SOD1\_Mut: FAM-5'-CAAA-GATCGTGTGGCCAC-3') (SEQ ID NO:75). Furthermore the 18S ribosomal RNA gene was chosen as the endogenous control using the following primers and probes: 18S-F: 5'-CGCTCCACCAACTAAGAACG-3' (SEQ ID NO:76), 18S-R: 5'-CTCAACACGGGAAACCTCAC-3' (SEQ ID NO:77), and 18S-probe: SYBR-5'-GGTGGTGG-3' (SEQ ID NO:78). Separate mixtures for mutated SOD1, wild type SOD1, and 18S were prepared and consisted of 5  $\mu$ L 2 $\times$  TaqMan® Universal PCR Master Mix, 0.3  $\mu$ L of each primer (10  $\mu$ M), 0.25  $\mu$ L probe (5  $\mu$ M), 2  $\mu$ L of a 10 fold diluted cDNA template, or in the case of 18s, 2  $\mu$ L of a 10,000 fold diluted cDNA template, and H<sub>2</sub>O to a final volume of 10  $\mu$ L. Real-time PCR was accomplished under the following conditions: 2 min at 50° C., 10 min at 95° C., 40 cycles of 95° C. for 15 sec and 60° C. for 1 min. All PCRs were performed in triplicate. The cycle threshold (Ct) values corresponding to the PCR cycle number at which fluorescence emission in real time reaches a threshold above baseline emission were determined in the software SDS 2.2 (PE Applied Biosystems). To compare expression levels of wild type SOD1 in the various tissues relative mRNA template concentrations were calculated using the standard curve method.

#### Southern Blot Analysis

Transgene integration was determined by Southern blot analysis of DNA from musculus longissimus dorsi from the two affected boars. 15  $\mu$ g of genomic DNA, undigested, Pvu II-digested, and double digested with Pvu II and Bam HI were separated on a 0.9% agarose gel, blotted to a nylon membrane and probed with [32P]-labelled SOD1 cDNA fragment constituting approximately 450 bp spanning the entire porcine SOD1 coding region derived from PCR amplification followed by nick translation. Genomic DNA from a healthy wild type pig was subjected to the same treatment as DNA from the two boars and has been included as control. Hybridization was accomplished in a hybridization buffer containing 5 $\times$ Denhardt's solution and 6 $\times$ SSC at 68° C. for 16 hours.

#### SOD Analysis

The SOD activity was determined with the Superoxide Dismutase assay kit (Cayman Chemicals, Ann Arbor, Mich.), based on the ability of SOD1 to inhibit the reduction of tetrazolium salt induced by xanthine-xanthine oxidase as described [47], and was accomplished according to manufactures recommendations using serum from the two diseased pigs and one control. One unit of SOD is defined as the amount of enzyme needed to exhibit 50% dismutation of the superoxide radical, O<sub>2</sub>·<sup>-</sup>, and a solution of bovine erythrocyte SOD (Cu/Zn was used as standard. Serum samples have been extracted on regular basis for 9 month yielding a total 19 samples from boar 4905, 17 from 4908, and 19 from the control pig, which all were included in the assay. The absorbance was read at 450 nm using a plate reader. The serum protein content was determined with a standard protein assay based on bicinchoninic acid (BCA) using manufactures recommendations (Pierce, Rockford, Ill.) employing bovine serum albumin as a reference and measuring the absorbance at 562 nm.

#### Histopathology

For examination of muscle tissue samples were taken from the center of longissimus dorsi above the curvature of the last rib from the two affected boars (4905 and 4908) and two wild type controls (147 and 3713). The size of the sample was app. 5 $\times$ 5 $\times$ 1 cm. At excision the samples were frozen in isopentane cooled in liquid nitrogen to minimize internal freeze artefacts. Transverse serial sections (10  $\mu$ m) were cut in a cryostat at -20° C. and collected on lysine coated cover slips. The sections were immunohistochemically stained for slow myosin heavy chain (MHC) isoform (Catalogue no. CRL-2043, American Type Culture Collection) to identify type I fibres. A description of the methods used for the immunohistochemical stainings is given in Pedersen et al. (2001) [48]. The architecture of fibre types in pig muscles is unique as type I and IIA fibres are located in clusters. For the analysis we have counted the number of fibres within clusters as this is less affected by growth or differences in size of animals and compared the distributional characteristics of fibres within clusters. In the analysis clusters of type I fibres have been included.

For histopathological investigation of medulla spinalis both affected boars, 4905 and 4908, as well as two wild type boars, 147 and 3713, at approximately the same age were employed. After immersion fixation of cervical medulla spinalis in 4% paraformaldehyde, the tissues were embedded in paraffin and sectioned into slices of 5  $\mu$ m. Sections were stained with 7 anti-SOD1 peptide antibodies. However, only the 100-115 anti SOD1 peptide antibody were specific for the porcine SOD1, and is therefore, the one used in this work. The immunohistochemistry was performed using the Ventana immunohistochemistry system.

#### Statistics

Variation in number of type I muscle fibers in musculus longissimus dorsi between the two affected boars (4905 and 4908) and controls (3713 and 147) were tested with respect to statistical significance employing students t-test considering unequal variances ( $\alpha=0.05$ ), since data approaches the underlying assumption of normality.

#### Description of the Porcine Phenotype

Initially, the first signs of phenotypic alterations were appearing in one of the boars, 4905, at the age of seven months. The boar was slightly ataxic and showed reduced proprioception and it preferred to lie down. The symptoms became gradually worse and at the age of ten months the boar showed fasciculation when getting up and laying down. Furthermore, the boar had pronounced, abnormal itching reflexes and at the age of 15 months the boar was sacrificed since it was nearly unable to get up without help. The other boar, 4908 got slightly symptomatic at the age of approximately 8 months, where it like the other boar, was slightly ataxic and showed reduced proprioception. One month later it showed fasciculations, which turned gradually worse and at the age of 12 month, these fasciculations was very severe and continuously present when the boar was standing in an upright position. Furthermore, this boar showed abnormal tongue movements. At the age of 14 months the boar was sacrificed. Both of the boars were all the time able to accomplish basic necessities of life such as eating, drinking, and urinating without any help.

#### Southern Blot Analysis

To establish whether integration of the transgene had occurred Southern blot analysis was performed on tissue from musculus longissimus dorsi from the two affected boars and on wild type control. The used probe spans the entire SOD1 coding region, constituting approximately 450 bp. However, no detectable bands can be seen in any of the

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samples constituting undigested, Pvu II digested and Pvu II and BAM HI double digested DNA from boar 4905 and 4908 and the wild type pig showing that genomic integration has not occurred. Furthermore, under the same conditions the ~five copy fragment control harboring the SOD1 cDNA, were clearly detected (lane 11 and 12, in FIG. 10), suggesting that the SOD1 cDNA is markedly underrepresented in the genome (<1 copy per genome).

#### PCR Analysis

To further establish if the transgene could be present, for instance as an extrachromosomal entity, which has been demonstrated in a recent study [49], both the two affected boars and the five littermates were checked for the presence of transgene using DNA purified from blood as a template. Primers enabling both the amplification of the wild type genomic SOD1 fragment spanning exon 3 to exon 4, yielding approximately 800 bp, and the mutated SOD1 DNA fragment, yielding approximately 200 bp were employed. FIG. 11 shows that apart from the positive control only the 800 bp DNA fragment arising from the endogenous SOD1 was amplified. This indicates that none of the seven animals harbour the fragment used during the SMGT procedure. Furthermore, also DNA extracted from the tails of the seven animals has been subjected to PCR analysis, yielding also negative results regarding the occurrence of the mutated SOD1.

Still, it can not be ruled out that a minor fraction of the cells harbours the construct, applied in the SMGT procedure, possibly stored as an extrachromosomal fragment; however this is beyond our detection limit. Furthermore, the presence of transgene in other tissues in a minor fraction of the cells ruled out either; however since PCR amplification in various tissues of the sacrificed pigs did not give rise to any consistent amplification of the DNA fragment used in the SMGT procedure only a minor fraction of the total number of cells include said fragment.

#### SOD1 Expression Analysis

Expression of the SOD1 construct harbouring the Gly93Arg substitution was accomplished by quantitative RT-PCR using TaqMan probes spanning the DNA region harbouring the substitution, and hence separate RT-PCR's were conducted regarding the wild type SOD1 mRNA and the mutagenised SOD1 mRNA from heart, kidney, liver, lung, spleen, medulla spinalis, frontal cortex, parietal cortex, musculus longissimus dorsi, musculus semitendinosus left side, musculus semitendinosus right side, musculus semibranosus left side, and musculus semibranosus from the two affected boars and from the two wild type controls and assayed for the presence of the mutagenised SOD1 transcript or alternatively altered endogenous SOD1 levels. Furthermore, the mutagenised SOD1 fragment was included in the expression analysis to ensure that the SOD1 probe matching the mutagenised fragment was perfectly suited to detect any transcript. FIG. 12B shows amplification of the mutagenised fragment in various concentrations emphasizing, that the probe is suitable for detection of mutagenised transcripts. However, since no difference is seen between the amplification curves, representing of the affected boars and the controls in any of the 12 tissues it is concluded that mutagenised transcripts are not present in the affected boars, FIG. 12. Although a wide variety of tissues have been included, it can not be ruled out that expression of the transgene could possibly be present in other tissues or at very low levels which could not be detected in this assay.

FIG. 12A shows the amplification curves using the probe detecting the SOD1 wild type transcript. This reveals that the SOD1 probe detects the SOD1 transcript, even though some background amplification would be present in case of pos-

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sible SOD1 mutant transcript, since an amplification curve is present using the SOD1 mutagenised fragment (pink curve in FIG. 12A). However, since no mutagenised transcript could be detected, this is not considered in the real time analysis in FIG. 12C. The real time analysis reveals no differences in the endogenous SOD1 expression levels between the two wild type boars and the two affected boars in any of the analysed tissues. However, large inter tissue variations are present, which is also the case between tissues. The highest expression levels are seen in liver and kidney, which is also in agreement with studies performed on human tissues [50].

#### SOD Activity in Serum

SOD1 activity was detected spectrophotometrically in serum as a measurement for the SOD1 to inhibit the reduction of tetrazolium salt induced by xanthine-xanthine oxidase [47] and was not corrected for Mn-SOD, meaning that the activities in FIG. 13 represent the total SOD activity in serum. However, since Mn-SOD accounts for a minor fraction of the total SOD activity in serum [51] it is not likely that it would mask possible differences between affected boars and the control. The SOD activity levels in serum of the two transgenic affected boars was approximately at the same level as the control boar during the time course recorded, and no significant variation across time (from October 2005-August 2006) has been revealed, FIG. 13.

Furthermore, proteome analysis employing protein extracts from liver and musculus longissimus dorsi failed to detect any mutagenised SOD1 protein in the two transgenic boars (data not shown).

#### Histopathological Investigations

Since the nature of muscle fibers may be used to assess disease progression of ALS the clusters including type I muscle fibers in musculus longissimus dorsi were examined regarding the number of fibers in each cluster. This investigation revealed that the frequencies of type I fibers in the two affected boars are significantly decreased in comparison to controls, FIG. 14. Statistical evaluation reveals P-values of  $3 \times 10^{-6}$  and  $2 \times 10^{-5}$  for 4905 and 4908, with respect to the control boar, 147, emphasizing highly significant differences. Furthermore a P-value of 0.08 reveals that the two controls are not statistically different, which is also the case for the two affected boars,  $P=0.11$ . The stainings, FIG. 14, further highlights the large differences in number of type I fibers, both regarding the size of the clusters and the absolute number, which is also reduced in the two transgenic boars.

Sections from cervical spinal cord of the two affected boars and two age matched wild type boars were stained with various peptide antibodies raised against human SOD1. However, only the 100-115 anti-SOD1 peptide antibody proved to be specific with respect to porcine SOD1. FIG. 15 shows a motorneuron from the spinal cord of both an affected boar (4908) and the age matched control boar (147). In FIG. 15A) showing a motor neuron from the affected boar, SOD1 stainings are seen in the motor axon, most likely arising from SOD1 inclusions. In comparison no stainings are seen in the axon of the control. Furthermore, in FIG. 15A large fluorescent compartments are seen in the neuropil which are not present in the control either.

#### Example 2

##### A Transgenic Pig Model for Parkinson's Disease

##### Cloning of the Porcine SNCA cDNA

The full-length porcine  $\alpha$ -synuclein (SNCA) cDNA was isolated from cerebellum by a combination of RT-PCR and RACE. Initially, blast searches using the human SNCA

cDNA sequence were carried out with GenBank (<http://www.ncbi.nlm.nih.gov/Genbank/index.html>) and with the porcine EST data bank at The Danish Institute of Agricultural Sciences (DIAS). Sequence similarity search was performed with gapped alignment using NCBI Blastall with options blastn, minimum value 10-8. The porcine cDNAs thus identified were used to derive oligonucleotide primers for cloning and as queries for further searches in the local genomic DIAS sequence database.

The pig cerebellum tissue used for RT-PCR cloning of porcine SNCA was obtained from an adult pig. After removal, tissue was dissected and pulverized in liquid nitrogen. Total RNA was isolated by the RNeasy method (Qiagen). The integrity of the RNA samples was verified by ethidium bromide staining of the ribosomal RNA on 1% agarose gels.

The porcine SNCA cDNA presented here was isolated using an RT-PCR cloning approach. Synthesis of cDNA was conducted with 5 µg of total RNA isolated from pig cerebellum using SuperScript II RNase H-reverse transcriptase (Invitrogen). The cDNA synthesis was initiated by heating of total RNA, oligo(dT) 12-18 primer, dNTP at 65° C. for 5 min followed by addition of 200 units reverse transcriptase and then incubation at 42° C. for 50 min followed by 70° C. for 15 min.

The RT-PCR reaction mix contained: 2.5 µl cDNA, 1.5 mM MgCl<sub>2</sub>, 0.2 mM dNTP, 0.5 µM of each primer SNCA-F: 5'-CCATGGATGTATTCATGAAAGGACTTTCAA-3' (SEQ ID NO:79) and SNCA-R: 5'-CTTCCGGCTCAT-AGTCTTGATACCC-3' (SEQ ID NO:80), and 1 U Phusion DNA polymerase (Finnzymes), in a total volume of 25 µl. PCR amplification was carried out in the total volume using the following program: Denaturation at 94° C. for 2 min., 10 cycles of 94° C. for 15 s, 55° C. for 30 s, 72° C. for 40 s, followed by 25 cycles of 94° C. for 15 s, 60° C. for 30 s, 72° C. for 40 s. The PCR program was concluded by an extension at 72° C. for 7 min. Twentyfive microlitres of the amplification product was applied to a 1% agarose gel and visualized after electrophoresis by ethidium bromide staining. A fluorescent band of approx. 400 bp was cut out and eluted using the Qiaquick Gel Extraction kit from Qiagen. The eluted PCR product was cloned directly into the pCR TOPO 2.1 vector (Invitrogen) and sequenced in both directions.

To obtain a full-length coding SNCA cDNA, sense and antisense primers derived from the isolated SNCA fragment were used in 5' and 3' RACE (rapid amplification of cDNA ends) experiments. A sense SNCA specific primer was used in combination with a kit anchor primer (Roche Molecular Biochemicals). In brief, for 3'-RACE, an oligodT reverse transcription oligonucleotide primer, 5'-GACCACGCGTATCGATGTCGACTTTTTTTTTTTTTTTT-3' (V=A, C or G) (SEQ ID NO: 81) was used in a reverse transcription reaction. The resultant SNCA cDNA was used as a template for PCR amplification employing the proof-reading DNA polymerase Phusion (Finnzymes), in combination with a kit PCR anchor primer: 5'-GAAAACGCGTATCGATGTTCTCGAC-3' (SEQ ID NO:82) and a gene-specific primer SNCA-F: 5'-CCATGGATGTATTCATGAAAGGACTTTCAA-3' (SEQ ID NO:83). PCR products were recovered as described above, cloned into the pCR TOPO2.1 vector and sequenced. one PCR amplicon of approx. 800 bp contained a DNA fragment that showed homology to SNCA and which also matched the sequence of the partial SNCA cDNA where the sequences overlapped. For 5'-RACE a reverse transcription oligonucleotide primer, SNCA5-it1: 5'-GGATCCTACATAGAGCACACCCTC-3' (SEQ ID NO:84) was used in a reverse transcription reaction. The synthesized SNCA cDNA was used as a template for PCR amplification employing

Phusion DNA polymerase (Finnzymes), in combination with a kit PCR anchor primer: 5'-GAAAACGCGTATCGATGTTCTCGAC-3' (SEQ ID NO:85) and a gene-specific primer, SNCA5-it2: 5'-TCCCGCTGCTTCTGCCACACCCTG-3' (SEQ ID NO:86). PCR products were recovered as described above, cloned into the pCR TOPO2.1 vector and sequenced. one PCR product contained a DNA fragment that showed homology to SNCA and also matched the sequence of the partial SNCA cDNA where the sequences overlapped.

The interconnectedness between the original cDNA clone and the 5'- and 3'-RACE sequences was confirmed by PCR with the primers SNCA5-F: 5'-CAGTCTGTTAGGGGAGGAGCTTATTC-3' (SEQ ID NO:87) and SNCA-it3: 5'-CTATAGTTAATATTTATAGGTGCATAGTTCC-3' (SEQ ID NO:88). PCR amplification was carried out in the total volume using the following program: Denaturation at 95° C. for 2 min., 10 cycles of touchdown (-0.5° C. per cycle) 95° C. for 20 s, 60° C. for 30 s, 72° C. for 45 s, followed by 25 cycles of 95° C. for 20 s, 55° C. for 30 s, 72° C. for 45 s. The PCR program was concluded by an extension at 72° C. for 5 min.

DNA sequencing was performed employing the dideoxy chain termination method using BigDye terminator cycle sequencing kit with AmpliTaq DNA polymerase FS (PE Applied Biosystems). The sequencing analysis was performed on an automated DNA sequencer (ABI PRISM™ Genetic Analyzer Model 3730xl, PE Applied Biosystems). Traces were aligned and visualized using the SEQUENCHER version 4.0.5 for Windows (Gene Codes Corporation).

#### 30 Characterization of the Porcine SNCA cDNA

The SNCA cDNA was amplified by the reverse transcriptase polymerase chain reaction (RT-PCR) using oligonucleotide primers derived from in silico sequences. Partial porcine SNCA EST sequences identified in the DIAS EST library were used to derive primers for RT-PCR amplification of the SNCA cDNA. A 420 bp fragment was obtained which showed a high level of homology to published SNCA sequences. Sense and antisense primers were designed from this sequence and used for 5' and 3'-RACE experiments. With one round of PCR a SNCA cDNA covering the coding and 3'UTR sequence was obtained. Similarly, one round of PCR generated the missing 5'UTR sequence. To confirm that the obtained porcine SNCA fragments were interconnected, a PCR reaction using primers covering the near full-length coding sequence of was performed. This resulted in the 982 bp cDNA sequence shown in FIG. 16.

The identity of the porcine SNCA cDNA was established by comparing the deduced polypeptide sequence with other isolated alpha-synuclein proteins. The porcine SNCA cDNA (GenBank Access. No. DQ073395) is 982 bp in length with the translational start site at nucleotide 104 and the TAA stop codon at nucleotide 524. The open reading frame (ORF) of SsSNCA has a G+C content of 50% and it encodes a polypeptide of 140 amino acids with an estimated molecular mass of 14.5 kDa and a pI of 4.6. The encoded porcine  $\alpha$ -synuclein protein contains the characteristic motifs of other  $\alpha$ -synuclein proteins: five imperfect repeats with a core consensus sequence KTKEGV distributed from the amino terminus to the central part of the protein. As for other  $\alpha$ -synucleins eleven central hydrophobic amino acids are missing compared to the homologous  $\beta$ -synuclein and  $\gamma$ -synuclein.

Amino acid sequence similarity between porcine  $\alpha$ -synuclein and other published mammalian  $\alpha$ -synuclein proteins was determined by the Clustal method. Multiple alignment of  $\alpha$ -synuclein amino acids sequences from pig, human, mouse and rat, cow, chicken and *Xenopus* (FIG. 17) revealed a very high overall homology. Interestingly, it was found that the

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amino acid in position 53 which is an alanine in human is a threonine residue in all other species. This particular alanine residue is found substituted to a threonine (Ala53Thr) in familial Parkinsonism.

A very high degree of identity between porcine  $\alpha$ -synuclein and most other alpha-synuclein proteins was found. The encoded pig  $\alpha$ -synuclein polypeptide exhibits significant sequence identity to human  $\alpha$ -synuclein (98%), cow  $\alpha$ -synuclein (96%) and mouse and rat  $\alpha$ -synuclein (both 94%). The lowest amino acid identity between pig  $\alpha$ -synuclein and other  $\alpha$ -synuclein proteins was observed with the chicken  $\alpha$ -synuclein (84%) and the *Xenopus* sequence (80%). See FIG. 18 for a phylogenetic tree. The Prosite Web site (<http://www.expasy.ch/prosite/>) was used to analyze the 140 amino acid porcine  $\alpha$ -synuclein protein sequence and predicted a molecular weight of 14.5 kDa and identified potential post translational modifications. These include one casein kinase II phosphorylation site, one tyrosine kinase phosphorylation site and five putative myristoylation sites.

Site Directed Mutagenesis of Porcine SNCA

In order to introduce the Ala30Pro mutation into the porcine SCNA, site directed mutagenesis was performed employing the QuickChange® XL Site-Directed Mutagenesis Kit (Stratagene) and accomplished in accordance with manufactures recommendation applying the following primers:

SNCA-A30P-F: (SEQ ID NO: 89)  
5'-GGGTGTGTCGACAAGCACCGGAAAGACAAAGAG-3'

SNCA-A30P-R: (SEQ ID NO: 90)  
5'-CTCTTTTGTCTTCCCGGTGCTTCTGCCACACCC-3'

The PCR conditions were: Denaturation at 95° C. for 1 min., 18 cycles of 95° C. for 50 s, 60° C. for 50 s and 68° C. for 6 min. The PCR program was concluded by an extension at 68° C. for 7 min.

To ensure that the mutation of interest was integrated in the porcine SNCA gene, several colonies were picked and grown overnight and plasmids were harvested and sequenced according to standard procedures. A plasmid containing the mutation was chosen as template for the subsequent procedures. Next, the plasmid containing the mutated SNCA cDNA was digested with KpnI and EcoRV releasing the SNCA fragment, which was now cloned into the KpnI and SmaI digested phCMV1 expression vector using standard protocols. XL10-Gold® Ultracompetent Cells (Invitrogen, CA) were transformed with the phCMV1 vector preparation and to ensure that the SNCA insert had integrated correctly into the phCMV1 vector colonies were grown in liquid LB-Amp and plasmids were purified and sequenced according to standard procedures.

Vector constructs containing correctly integrated mutagenized SNCA fragments were selected for following procedures.

Large-Scale SNCA DNA Preparation

In order to create DNA for incubation of sperm cells large scale PCR reactions were performed. The PCR reactions were carried out in a GeneAmp® PCR System 9700 (Applied Biosystems) in a final volume of 25  $\mu$ L consisting of 5  $\mu$ L 5 $\times$  Phusion HF buffer, 2  $\mu$ L dNTP (2.5 mM each) 0.63  $\mu$ L forward and reverse primer 5 pmol, 0.1  $\mu$ L Phusion DNA Polymerase (2 U/ $\mu$ L), 1  $\mu$ L SNCA-phCMV1 template, and 15.6  $\mu$ L H<sub>2</sub>O. The PCR reaction consisted of an initial denaturation at 98° C. for 30 sec followed by 30 cycles of denatur-

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ation for 10 sec at 98° C., annealing at 74° C. for 30 sec and elongation for 95 sec at 72° C. followed by a final elongation step at 72° C. for 7 min. The following primers were used to amplify the mutagenized SOD1 construct plus the flanking CMV promoter, intron sequence, and SV polyA, generating a fragment of approximately 2100 bp.

(SEQ ID NO: 91)  
phCMVF: 5'-GTCGGAACAGGAGAGCGCACGAGGG-3'

(SEQ ID NO: 92)  
phCMVR: 5'-GGGTGATGGTTCACGTAGTGGG-3'

In order to purify the generated PCR product a "High Pure PCR Product Purification Kit" (Roche) was applied. The suppliers' instructions were followed throughout the purification procedure. The PCR purified fragments were sequenced to check for errors in the sequence. See FIGS. 19 and 20.

Sperm Mediated Gene Transfer SMGT

Sperm Mediated Gene Transfer, Buffer:

In order to wash the porcine sperm cells and hence remove the sperm liquid, the following optimized buffer is applied:

| For 1 liter: |                           |
|--------------|---------------------------|
| 56.1 g       | Glucose                   |
| 3.5 g        | EDTA (2 H <sub>2</sub> O) |
| 3.5 g        | Sodium citrate            |
| 1.1 g        | Sodium bicarbonate        |

The components are dissolved in water and the solution is sterilized through a filter. Before the buffer is added to the sperm cells, 6 mg/ml BSA (Bovine Serum Albumine, Fraction V, Sigma) is added.

Selection of Sperm Donor Boars:

The selection of the sperm donor boars are crucial for the outcome of the procedure. A boar station (Hatting KS Viborg), have therefore been contacted and the boars of choice are selected so that the initial sperm motility is >90%. The sperm is collected in sterile 10 mL tubes and transported undiluted at a temperature not below 15° C. as this will cause damage to the sperm cells.

Washing Procedure:

The following procedure is accomplished as fast as possible (buffer is as indicated above):

5 mL sperm is transferred to a 50 mL Falcon tube  
5 mL buffer preheated to 37° C. is added

Mix by inverting the tubes

The solution is incubated for 5 min at room temperature (~22° C.)

40 mL buffer (room temperature) is added

Centrifuge at 800 g, for 10 min at 25° C.

Remove the supernatant

Resuspend the pellet in 50 mL buffer (room temperature)

Centrifuge at 800 g, for 10 min at 17° C.

Remove the supernatant

Carefully resuspend the pellet in the remaining buffer in the bottom of the Falcon tube.

Examination of the Sperm Cells:

In order to choose the correct donor cells, the sperm cells from the different boars are examined under a light microscope. The sperm cells originating from the boar having the highest sperm cell motility after the washing procedure are chosen. Next, the sperm cells from the boar of choice are counted.

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## DNA Uptake/Incubation:

10<sup>9</sup> sperm cells are diluted into 120 mL 17° C. buffer  
0.4 µg linearized DNA/10<sup>6</sup> sperm cells is added (that is, a  
total of 400 µg linearized DNA)

Incubate 100 min at 17° C.

To avoid sedimentation of the cells, invert the tube every 20 min

Transfer the tube to room temperature, and transport it, still at room temperature to stable facilities. This takes approx. 10 min. The incubated sperm cells are now ready to be applied in artificial insemination.

## Animals:

Two recipient sows (Danish Landrace×Yorkshire) at approximately 140 kg were selected due to their natural heating period and used for artificial insemination (1×10<sup>9</sup> DNA treated sperm/sow) meeting standard insemination procedures. Insemination was accomplished in the local stable areas at DIAS. Semen was collected from trained Landrace boars that have abstained for 2 days. Semen was treated according to aforementioned procedures. Both sows were examined for pregnancy 24 and 42 days after insemination, showing that only one of the sows was pregnant. Animal care and experimental procedures met local, national and European Union Guidelines.

## Test for Presence of the Transgene:

After 115 days (17 Jun. 2005) 10 normal looking piglets were born, 5 of these were boar piglets and 5 were sow piglets. One of the boar piglets died the following day (17 Jun. 2005). Blood samples were collected from the piglets in 6 mL EDTA blood collection tubes. Furthermore, blood from a wild type animal was collected as well and handled together with the 9 aforementioned animals. At a later stage semen was collected from selected animals and genomic DNA was isolated. DNA was purified according to standard blood purification procedures in special clean laboratories, in order to avoid any possible contamination.

The PCR reaction was performed in a total volume of 10 µL consisting of 1 µL 10×MgCl<sub>2</sub> free reaction buffer, 0.4 µL 50 mM MgCl<sub>2</sub>, 1 µL of both forward and reverse primer (10 pmol each), 0.5 µL dNTP mix, 0.5 µL DyNzyme EXT DNA polymerase (1 U/µL), 0.5 µL DNA template (50 ng), and 5.1 µL H<sub>2</sub>O.

Forward and reverse primer used for the above PCR procedure:

(SEQ ID NO: 93)  
PHCMV\_682F: 5'-GATTCCCCGTGCCAAGAGTG-3'

(SEQ ID NO: 94)  
SNCA-4R: 5'-TTGCCAGCTGATCCTTTTGCCAAAG-3'

The touchdown PCR reaction was accomplished in a GeneAmp® PCR System 9700 (Applied Biosystems) under the following conditions: Initial denaturation at 95° C. for 3 min, denaturation at 95° C. for 30 sec, touchdown from 62° C. to 57° C. with a decrement of 0.5° C. for 20 sec, followed by 1 min of elongation at 72° C. per cycle. Furthermore, 35 cycles of 30 sec denaturation at 95° C., 20 sec of annealing at 57° C., and 1 min of elongation at 72° C. was included together with a final elongation step at 72° C. for 7 min.

Blood samples were withdrawn from potentially transgenic piglets and PCR reactions were carried out on purified DNA as described above. FIG. 21 shows that all animals (4363-4371) are positive regarding the transgenic DNA fragment of 800 bp. However, mosaicism can not be ruled neither the possibility of the various animals having different copy numbers.

## Transgene in the Germ Cells:

In order to transfer the transgene to next generation it is important to ensure that the transgene is present in the germ

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cells. Therefore, DNA has been extracted from sperm cells from the two boars (4905 and 4908). The purification of DNA was accomplished using a standard purification procedure: Standard Purification Procedure:

300 µL of semen was washed in 1 mL 0.9% NaCl, followed by centrifugation for 5 min at 3000 rpm where after the supernatant was discarded. This step was repeated twice and 20 µL Pronase (20 mg/mL), 20 µL 1 M DTT, and 300 µL buffer S was added to each sample, where after these were left to incubate at room temperature overnight. Subsequently, 180 µL 6 M NaCl was added to each sample and shaken vigorously for approximately 20 seconds. The samples were now centrifuged for 15 min. at 10000 rpm and the supernatant was then carefully transferred to a new Eppendorf tube where the DNA was precipitated adding twice the volume of supernatant and centrifuged at 10000 rpm for 10 min. Subsequently the ethanol was removed and the DNA was air dried and resuspended in 300 µL of nuclease free water.

Buffer S composition: 10 mM Tris HCl (pH 8.0); 100 mM NaCl; 10 mM EDTA (pH 8.0); 0.5% SDS; H<sub>2</sub>O.

Presence of the modified SNCA transgene was examined in DNA purified from sperm cells from boars 4363-4371. As shown in FIG. 22 all boars harbored the transgene in the sperm cells. A PCR of the expected size of 800 bp can be observed in for all animals although at differential amounts. Phenotypic Characterization of Boar #4363

First symptoms were observed in three boars at the age of 17 months. The pigs were examined by Knud Larsen and veterinarian Keld Dahl Winter (Danish Meat). One boar #4363 had the most pronounced symptoms. When standing the boar showed a strongly upward curved (convex) back. Loss of muscle tissue was observed in musculus longissimus dorsi left side while the right side was unaffected. During activity permanent tremor of the tail was observed. More pronounced tremor was seen in the neck especially when the head was raised. Tremor was also visible in the tail and in ear tips. The tremor was intermittent and disappeared partly when the boar was at rest. The tremor in head and neck was worsened when the boar was surprised by visitors and by rising of the head. The boar appeared with a rigid body posture, moved very slowly and did not turn around when people were circling around it. This is not a normal behaviour. The coordination of the limbs was fully normal. However, the movements were very slow. The general state of health was largely unaffected and the boar did not show any signs of pain.

One month later boar #4363 was examined. Tremor of head, neck and tail had increased significantly and were now present partly as resting tremor. The pronounced tremor symptoms have not been observed in any earlier described syndromes in pigs (pers. comm. Keld Dahl Winter). The boar's movements were very slow and considered inhibitory as no turning towards people approaching at the tail was seen. A normal healthy pig would immediately turn towards an arriving person. Since the latest examination one month earlier the muscular atrophy had increased and spread to both sides of the back. The backline had become more visible and the neural spines were more protruding.

Sixteen days later the boar #4363 was sacrificed and dissected for further analyses.

## Pathological Examination of Boar #4363

Boar #4363 was sacrificed and dissected. Samples from different organs such as heart, liver, kidney, lung, spleen were collected together with samples from testis and selected muscles (musculus longissimus dorsi). Also the brain was taken out and divides into to halves, both were dissected into discrete regions and either snap-frozen or fixed in formaldehyde. After three weeks fixation different brain samples were embedded in paraffin, sliced with a microtome and subjected to different stainings. Nissl AMG-staining of thin-layer sections from substantia nigra revealed presence of neurons but

most of the neurons were shrunken with lacunae and no clear segregation between the nucleus, nucleolus and cytoplasm (FIG. 23). Similarly, as shown in FIG. 24, HE-staining also demonstrated shrunken neurons with numerous lacunae (holes) which is a clear indication of neural degeneration.

A staining procedure for tyrosine hydrolase (TH) was also carried out on the thin layer sections. The results showed as illustrated in FIG. 25, that 1) The number of dopaminergic cells seemed to be reduced and 2) The remaining dopaminergic cells and neuropil seemed to be more rough and unordered.

For comparison a brain sample from a mini-pig was also examined for TH staining. Numerous dopaminergic cells were observed.

A GFAB staining revealed an intense staining in the mesencephalon of boar #4363, an indication of pronounced inflammation and gliosis (FIG. 26). Numerous astrocytes are noted indicative of active inflammation and reactive gliosis. Very interestingly, a specific antibody staining for  $\alpha$ -synuclein, using Ab raised against human  $\alpha$ -synuclein, revealed patches of large  $\alpha$ -synuclein aggregates throughout the mesencephalon (FIG. 27).  $\alpha$ -synuclein is located in the cell bodies and extracellular surroundings

In conclusion, all pathological examinations of boar #4363 are clearly indicative for PD. However, no classical Lewy bodies are observed. Lewy bodies are a cardinal symptom of PD and presence of Lb is needed to recapitulate the development and progression of PD. The explanation for the missing LBs could easily be that boar #4363 was sacrificed too early in the progression of disease. As the boar was at the age of 18 months and showing a large row of the clinical symptoms of PD but without complete resting tremor it was what could be expected at this particular stage.

FIG. 23 shows a Nissl staining of substantia nigra isolated from boar #4363. The figures clearly demonstrate that there are fewer cells present than expected from a normal healthy individual. Furthermore, neurons in substantia nigra look abnormal and also presence of cytoplasmic vacuoles and shrinking of cells is indicative of an abnormal condition. Lewy bodies are not visible in this staining.

### Example 3

#### A Transgenic Pig Model Animal of Alzheimer's Disease

##### PSEN1 and PSEN2 Isolation and Sequencing

Pig brain, lymphocyte, and liver RNA was isolated with the TRI-reagent (Sigma). For RT-PCR of PSEN1 the following primers were used (PSEN1 forward, 5'-TGGAGGAGAACAC-

CATGAAAGAAAAG-3' (SEQ ID NO: 95); PSEN1-forward-EcoR1 5'-GGGGAATTCTGGAGGAGAACACATGAAAGAAAG-3' (SEQ ID NO:96); PSEN1reverseEcoR1, 5'-GGGGAATTCCCTGACTTTGTTAGATGTGGACAC-3' (SEQ ID NO:97). The RT-PCR reaction was incubated at 50° C. for 60 min with the reverse primer followed by PCR with the PSEN1 forward-EcoR1 and PSEN1 reverse-EcoR1 primers at conditions (94° C. for 3 min, 35 cycles of; 94° C., 45 sec; 62° C., 30 sec; 68° C., 2 min, followed by a final elongation step at 68° C. for 7 min). Amplified DNA fragments were purified from agarose gels and either directly sequenced or EcoR1 cloned into pCDNA3 followed by DNA purification and sequencing. For RT-PCR of PSEN2 the following primers were used (PSEN2-forward, 5'-GCCATGCTCACTTTCATGGC-3'; PSEN2-reverse (SEQ ID NO: 98), 5'-CACGACTGCGTCCAGTGACC-3' (SEQ ID NO: 99). The reverse transcription reaction was accomplished using the Invitrogen reverse transcription system (Invitrogen) and 5  $\mu$ g of total-RNA according to the manufacturer's instructions. Subsequently, the PCR reaction was carried out at the following conditions: (94° C. for 3 min, 35 cycles of; 94° C., 45 sec; 60° C., 30 sec; 68° C., 2 min, followed by a final elongation step at 68° C. for 7 min). Amplified DNA fragments were purified from agarose gels and either directly sequenced or cloned into pCR® 2.1-TOPO® Vector (Invitrogen) followed by DNA purification and sequencing. The porcine pSEN1 and pSEN2 cDNA sequences were submitted to GenBank (Accession numbers DQ853416, and DQ853415, respectively)

##### BAC-Hybridisation

Radioactive probes were generated employing the nick translation kit from Invitrogen which incorporated [ $\alpha$ -32P] dCTP into the PCR generated PSEN1-exon8 fragment. High-density colony BAC filters (a generous gift from Dr. P. D. Jong) of the porcine genome were screened with the PSEN1-exon8 probe. The filters were pre-hybridized, hybridized, washed and autoradiographed according to standard methods. Positive spots were localised and BAC DNA of positive clones was isolated using the alkaline lysis method described by Zhang et al. (1996). BAC clone 388G9 contained the PSEN1 genomic sequence and was used for intronic sequence generation.

##### Generation of Intron Sequence Information

The BAC clone 388G9 was sequenced with primers located in exons 5, 7, 8 and 9 and pointing towards the intronic sequences. Table 8 shows the applied primers. All exon and flanking intronic sequences were deposited as a gapped submission to GenBank (Accession number DQ86246).

TABLE 8

| Sequences of primers and real time PCR probes |                               |            |                |
|-----------------------------------------------|-------------------------------|------------|----------------|
| Primer and probes                             | Sequence                      | SEQ ID NO: | Application    |
| PS1 Exon 5 forward primer1                    | 5'-GGAGGTGGTAATGTGGTTGG-3'    | 100        | BAC sequencing |
| PS1 Exon 5 reverse primer1                    | 5'-CCAACCATAAGAAGAACTGGG-3'   | 101        | BAC sequencing |
| PS1 Exon 7 forward primer1                    | 5'-CCTATAACGTTGCCATGGATTAC-3' | 102        | BAC sequencing |
| PS1 exon 7 reverse primer1                    | 5'-CACAGCCAAGATGAGCCAC-3'     | 103        | BAC sequencing |

TABLE 8-continued

| Sequences of primers and real time PCR probes |                                     |            |                |
|-----------------------------------------------|-------------------------------------|------------|----------------|
| Primer and probes                             | Sequence                            | SEQ ID NO: | Application    |
| PS1 Exon 8 forward primer1                    | 5'-GCTGGTTGAAACAGCTCAGGAG-3'        | 104        | BAC sequencing |
| PS1 Exon 8 reverse primer1                    | 5'-CCAGCAAACGAAGTGGGCCATTG-3'       | 105        | BAC sequencing |
| PS1 Exon 9 forward primer1                    | 5'-CAACAATGGTGTGGTTGGTG-3'          | 106        | BAC sequencing |
| PS1 Exon 9 reverse primer1                    | 5'-GGATACCTTCCTTTGGGCTTC-3'         | 107        | BAC sequencing |
| PS1 Exon 5 forward primer2                    | 5'-GAGACTTAGCTGGGGTTTGTG-3'         | 108        | SNP screening  |
| PS1 Exon 5 reverse primer2                    | 5'-CCAAGTAAGGTGAGACAGGAAAACC-3'     | 109        | SNP screening  |
| PS1 Exon 7 forward primer2                    | 5'-GCTACGAGTATGAAGTGGGATATG-3'      | 110        | SNP screening  |
| PS1 exon 7 reverse primer2                    | 5'-CCAGGAGTCAAGATAACTGG-3'          | 111        | SNP screening  |
| PS1 Exon 8 forward primer2                    | 5'-CCACCATCTGTTTACCTGCTA-3'         | 112        | SNP screening  |
| PS1 Exon 8 reverse primer2                    | 5'-GGCCATCATTACATGTGTTTG-3'         | 113        | SNP screening  |
| PS1 Exon 9 forward primer2                    | 5'-GGTGACATTAAGAAGTTTGGTGACTTG-3'   | 114        | SNP screening  |
| PS1 Exon 9 reverse primer2                    | 5'-GGGTGTTACCACAGCTTGGAG-3'         | 115        | SNP screening  |
| PS1 forward primer                            | 5'-GTGATTTTCAGTATACGATTTAGTGGCTG-3' | 116        | Real Time PCR  |
| PS1 reverse primer                            | 5'-CACCAACCACACCATTGTTGAC-3'        | 117        | Real Time PCR  |
| PS1 MGB probe                                 | 5'-VIC-TTGTGTCCAAATGGC-3'           | 118        | Real Time PCR  |
| PS2 forward primer                            | 5'-GGAGGAAAGGGCGTGAAG-3'            | 119        | Real Time PCR  |
| PS2 reverse primer                            | 5'-CACAAACCGATGAGGATGGC-3'          | 120        | Real Time PCR  |
| PS2 MGB probe                                 | 5'-VIC-CTGGAACACCACGCTGG-3'         | 121        | Real Time PCR  |
| GAPDH forward primer                          | 5'-GACTCATGACCACGGTCCATG-3'         | 122        | Real Time PCR  |
| GAPDH reverse primer                          | 5'-GTCAGATCCACAACCGACACG-3'         | 123        | Real Time PCR  |
| GAPDH MGB probe                               | 5'-VIC-CATCACTGCCACCCAGA-3'         | 124        | Real Time PCR  |

### SNP Screening

Exons 5, 7, 8 and 9 and flanking intron sequences were amplified by PCR (primers listed in table 8 under SNP-screening application). Exon 5 and flanking intron sequences were amplified at conditions 50 ng DNA; 94° C. for 3 min and 35 cycles; 94° C., 30 sec; 60° C., 20 sec; 72° C., 1 min. Exon 7 and flanking intron sequences were amplified at conditions 50 ng DNA; 94° C. for 3 min and 35 cycles; 94° C., 20 sec; 58° C., 20 sec; 72° C., 1 min. Exon 8 and flanking intron sequences were amplified at conditions 50 ng DNA; 94° C. for 3 min and 35 cycles; 94° C., 45 sec; 64° C., 30 sec; 72° C., 1 min. Exon 9 and the flanking intron sequences were amplified at conditions 50 ng DNA; 94° C. for 3 min and 35 cycles; 94° C., 20 sec; 58° C., 20 sec; 72° C., 1 min. All PCR products were incubated with exozap at 37° C. for 1 hour and sequenced with the forward amplification primer. The

sequences were analyzed using PolyBace and checked manually in Consed.

### Hybrid Cell Mapping

A porcine-rodent somatic cell hybrid panel was used for physical mapping (Yerle et al., 1996) of both PSEN1 and PSEN2. For PSEN1 the exon 9 forward and reverse primers 2 were used for amplification of the probe fragment. For PSEN2 the PCR primers (PSEN2exon12F; 5'-GTTTGTGTCTGACCCTCCTGCTGC-3' (SEQ ID NO: 125) and PSEN2exon12R; 5'-CAGATGTAGAGCTGGTGGG-GAGG-3' (SEQ ID NO: 126)) were used for amplification of the probe fragment. PCR's were performed in a total volume of 10 µL containing 10 ng DNA, 1×PCR buffer, 2.5 mM of each dNTP, 5 pmol of each primer, and 0.5 U of Taq polymerase (Bioline) under the following conditions: 94° C. for 3 min; 35 cycles of 94° C. for 20 s, 65° C. for 20 s and 72° C. for 20 s, and a final elongation step for 5 min at 72° C.

## Immunohistochemistry

Fetal pig brains were immersion fixed in formalin and paraffin-embedded tissue blocks were produced from various brain regions. 10 micrometer coronal sections were then obtained on coated glass slides. The sections were deparaffinized and pretreated with proteinase K for 6 min. The slides were blocked with BSA (1 mg/ml) for 10 min. Immunohistochemical demonstration of PSEN1 and PSEN2 was performed using the EnVision+ System-HRP-DAB (DAKO). The anti-PSEN1 antibody was a rabbit polyclonal antiserum 520 (a generous gift from Dr. Poul Fraser, Toronto, Canada) used in 1:100 dilution with incubation time 2 hours. The anti-PSEN2 antibody was the mouse monoclonal antibody, APS 26, used in 1:33 dilution with incubation time 2 hours (abcam). Nuclei were counterstained in haematoxylen solution. The slides were finally coverslipped with Faramount Aqueous Mounting Medium (DAKO).

## Real-Time Quantitative PCR Assay

Total RNA was isolated from cerebellum, frontal cortex, hippocampus, brainstem, and basal ganglia from 60, 80, 100, and 115 days old porcine fetuses using the TRI Reagent™ (Sigma) in compliance with the manufacturer's instructions. Three separate tissues were applied for each type of tissue and time in gestation, yielding a total of 60 samples. The reverse transcription reaction was accomplished using an Invitrogen reverse transcription system (Invitrogen) and 5 µg of RNA according to the manufacturer's instructions. Quantitative real time PCR was performed using the TaqMan® assay and PCR amplification in an ABI-PE prism 7900 sequence detection system (PE Applied Biosystems). Primers and MGB probes were designed using the Primer Express Software 2.0 (PE Applied Biosystems), so that both forward and reverse primer spanned an exon-exon junction. The MGB probe was synthesized with VIC as a reporter dye. After an initial screening with different control genes GAPDH was chosen as the endogenous control and the MGB-probe was synthesized with VIC as a reporter dye. The primers and probes are detailed in table 8. Separate mixtures for PSEN1, PSEN2, and GAPDH were prepared and consisted of 5 µL 2× TaqMan® Universal PCR Master Mix, 0.3 µL of each primer (10 µM), 0.25 µL probe (5 µM), 2 µL of a 5-fold diluted cDNA template, and H<sub>2</sub>O to a final volume of 10 µL. Real-time PCR was done under the following conditions: 2 min at 50° C., 10 min at 95° C., 40 cycles of 95° C. for 15 sec and 60° C. for 1 min. For both PSEN1, PSEN2, and GAPDH PCRs were performed in triplicate. The cycle threshold (Ct) values corresponding to the PCR cycle number at which fluorescence emission in real time reaches a threshold above baseline emission were determined in SDS 2.2 (PE Applied Biosystems). To compare expression patterns in the various brain tissues at different developmental stages mRNA template concentrations for GAPDH, PSEN1, and PSEN2 were calculated using the standard curve method. Standard curves were constructed using 8 fold dilution of day 115 frontal cortex cDNA (4, 2, 1, 0.5, 0.25, 0.125, and 0.0625 µL). The mRNA quantity of each amplicon was calculated for each standard and experimental sample.

## Statistical Analysis

The equality of PSEN1 and PSEN2 expression levels between different time of gestation within the 5 sampled tissues were tested for statistical significance using the standalone software REST© [52]. The statistical model applied was the Pair Wise FEXT Reallocation Randomisation Test. The assumption regarding normal distribution of the data was avoided, and differences in expression between groups were assessed using the means for statistical significance by randomization. The level of probability was set at P<0.05 as

statistically significant and 50000 randomization steps were implemented in each comparison.

## Results

## PSEN1 and PSEN2 cDNA and Protein Sequence

To determine the cDNA sequence of porcine PSEN1 we designed a set of primers based on the conserved 5' and 3' untranslated regions between the rodent, bovine, and human PSEN1. Using RT-PCR, the cDNA representing the entire pig PSEN1 open reading frame was amplified, cloned and sequenced. The porcine cDNA was throughout the sequence homologous to human PSEN1 (90%) but only homologous to human PSEN2 in short dispersed regions. The porcine PSEN1 protein has a length of 467 amino acids, which compares well with the 467 amino acids of the human and mouse counterparts (FIG. 28). Multiple amino acid sequence alignment of PSEN1 revealed a 92% sequence identity between pig and human (FIG. 28). Furthermore, 34 changes were observed between the two sequences, 11 of these being conservative. Comparison of pig and mouse revealed a sequence identity of 89% and 16 of 50 amino acid changes were conservative. The cow PSEN1 has a length of 478 amino acids and a sequence identity of 94% to porcine, 12 of 28 changes being conservative, and hence, cow PSEN1 is the PSEN1 variant that shows the highest degree of identity to the porcine counterpart. Mutations in human PSEN1 can be cause Alzheimer's disease and it is noteworthy that none of the amino acid changes between pig and human are located in positions known to cause Alzheimer's disease. (FIG. 28) ([www.molgen.ua.ac.be/ADMutations](http://www.molgen.ua.ac.be/ADMutations)). By contrast, at position 318 where human PSEN1 contains a non-pathogenic polymorphism, E318G, a Q residue is present at the equivalent position in pig, cow, and mouse PSEN1 [53]. Two other non-pathogenic polymorphisms R35Q and F175S present in human PSEN1 are in the porcine PSEN1 R and F, respectively (FIG. 28) [54,55].

The human PSEN2 cDNA sequence was used to blast NCBI porcine databases as well as an in house porcine database allowing the design of primers corresponding to the 5'-end of the coding region and the 3'-non-coding region of the putative porcine PSEN2. The primers amplified a porcine cDNA fragment of approximately 1.4 kb and sequence analysis revealed high sequence homology with human PSEN2 (92%) but only homologous to human PSEN1 cDNA in small dispersed regions, demonstrating that the porcine orthologous of PSEN2 was identified. Analysis of the porcine PSEN2 open reading frame showed that the porcine PSEN2 protein consisted of 448 amino acid residues, as do the human and mouse orthologous (FIG. 29). Multiple amino acid sequence alignment of PSEN2 revealed 97.8% sequence identity between pig and human, and 1 of the observed 10 changes was conservative (FIG. 29). Comparison of pig and mouse showed a sequence identity of 95%, 8 of the 20 changes being conservative. The cow PSEN2 has a length of 449 amino acids and a sequence identity of 98.2%, where 4 of the 8 changes are of conservative. Thus, as observed for PSEN1, also the bovine PSEN2 protein shows the highest degree of identity to the porcine counterpart. Moreover, it should be noted that none of the observed changes between the sequences of the different species are located in PSEN2 positions identified to be mutated in Alzheimer's disease patients (FIG. 29) ([www.molgen.ua.ac.be/ADMutations](http://www.molgen.ua.ac.be/ADMutations)). At position 334 a non-pathogenic polymorphism, P334R, has been identified in human PSEN2 [54,56], and the proline residue was conserved in the porcine cDNA.

The amino acid sequence for porcine PSEN1 shows 64% identity to porcine PSEN2 and particularly amino acids in the transmembrane domains and the C-terminus are conserved

(data not shown). Also the two aspartic acid residues located in transmembrane domain 6 (D257 in PSEN1 and D263 in PSEN2) and transmembrane domain 7 (D385 in PSEN1 and D363 in PSEN2), and the "PAL" sequence, (P433, A434, L435 in PSEN1 and P414, A415, L416 in PSEN2) are conserved in both porcine PSEN1 and PSEN2, consistent with the essential role of these residues for the protease catalytic function of the presenilins [54,57,58].

#### Mapping of Porcine PSEN1 and PSEN2

A porcine-rodent somatic cell hybrid panel was used for the chromosomal mapping of porcine PSEN1 and PSEN2 genes (data not shown) [59]. Statistical evaluation applying the "Interpreting PCR data" program (<http://www.toulouse.inra.fr/lgc/pig/pcr/pcr.htm>) showed a chromosomal localization for the PSEN1 gene to chromosome 7q12-q26 with a probability of 0.4494 and a correlation of 1, and for the PSEN2 gene to chromosome 10p11-p16 with a probability of 0.9959 and a correlation of 0.7255. The specified regions of porcine chromosomes 7 and 10 have synteny with human chromosomes 14 and 1, respectively. This is in agreement with mapping of the human PSEN1 gene to 14q24.3 and the human PSEN2 gene to 1q31-q42.

#### Single Nucleotide Polymorphism Screening of Porcine PSEN1

To examine for genetic variation in porcine PSEN1, we resequenced exons 5, 7, 8, and 9 in a large animal material consisting of 900 Landrace/Yorkshire crossbreed sows and a pig breed panel consisting of 55 Landrace, Duroc, Yorkshire and Hampshire breeds. These exons were chosen for sequence analysis because they constitute "hotspots" for mutations in familial Alzheimer's disease. However, no SNP's were identified in the 4 exonic regions (data not shown). Next, we extended the polymorphism analysis to include intronic sequences, which identified a C/T SNP at position 58 in intron 8 (position 1163 in the sequence deposited in DQ86246) as well as two C/T polymorphisms at positions 52 and 92 and a G/A polymorphism at position 117 in intron 10 (positions 1535, 1575, and 1600 in the DQ86246). The genotyping data are summarized in table 9 and 10. All breeds except Hampshire were polymorphic in intron 8 and at positions 52 and 92 in intron 10, whereas only the Yorkshire breed was polymorphic at position 117 in intron 10. Genotype frequencies were in accordance with Hardy-Weinberg equilibrium, indicating that no selective disadvantage is associated with the SNPs.

#### PSEN Expression in the Developing Porcine Brain

PSEN1 and PSEN2 have been shown to be widely expressed during embryonic development and especially the expression profile in the CNS is well characterized [60-62]. Here, we measured the mRNA expression levels of PSEN1 and PSEN2 in hippocampus, cerebellum, frontal cortex, basal ganglia, and brain stem from dissected porcine foetus brains at days 60, 80, 100 and 115 of gestation using three biological samples for each of the time points. Day E115 corresponds to the normal day of birth. The PCR analyses were performed in triplicates. The requirement for a proper internal control gene was met by normalization to the GAPDH expression level to compensate for inter-PCR variation with respect to RNA integrity and sample loading. Although housekeeping gene expression has been reported to vary considerably within different tissues or treatments, we did not find any significant differential expression of GAPDH within the 5 different porcine brain tissues at the various developmental stages. The standard curve for the control GAPDH ( $R^2=0.98$ ), PSEN1 ( $R^2=0.98$ ), and PSEN2 ( $R^2=0.98$ ) were generated by plotting

Ct values versus log  $\mu$ L of cDNA. The slope of the regression line was used to calculate the amount of cDNA and thus mRNA in each sample. All GAPDH cDNA's generated almost identical Ct values within each type of tissue (data not shown) and accordingly the mRNA expression levels of PSEN1 and PSEN2 were normalized to the GAPDH expression level. Ethidium bromide-staining after real time PCR confirmed specific amplification of the relevant PCR products (data not shown).

PSEN1 and PSEN2 were expressed in all 5 tissues at the 4 time points evaluated. However, it should be noted, that for both PSEN1 and PSEN2 the mean standard deviation is considerable, reflecting a high heterogeneity among animals. In basal ganglia the PSEN1 expression levels did not vary significantly between the different times of gestation (FIG. 30). In frontal cortex, cerebellum, and hippocampus the PSEN1 expression level was significantly lower at day 115 of gestation compared to day 60 ( $P=0.001$ ,  $P=0.036$ , and  $P=0.003$ , respectively), yielding a reduction of 5, 2, and 3 times for the said tissues (FIG. 30). Furthermore, the reduction in PSEN1 expression in frontal cortex is also significant at day 80 compared to day 60 ( $P=0.003$ ). Similarly, PSEN1 expression is gradually reduced in hippocampus during the time period of gestation (FIG. 30). Moreover, the same tendency is seen in cerebellum, however the reduction in expression levels is only significant between day 100 and 115 ( $P=0.015$ ) and day 60 and 115 ( $P=0.036$ ).

For PSEN2 no differential expression was observed in frontal cortex. In hippocampus the only significant variation was seen as an increase in expression level between day 60 and 80 of gestation ( $P=0.015$ ) (FIG. 30). Also in the brain stem, PSEN2 is upregulated between day 60 and 80 of gestation ( $P=0.032$ ) (FIG. 30). In cerebellum and basal ganglia the expression levels of PSEN2 are up-regulated between day 80 and 100 ( $P=0.003$ , and  $P=0.03$ ) (FIG. 30). When comparing the overall expression levels of PSEN1 and PSEN2, an approximately three fold lower PSEN2 expression level is observed. In conclusion, the real time PCR analysis showed significant, albeit small, alterations in the expression levels of PSEN1 and PSEN2 mRNA in different brain compartments during embryonic brain development, which likely reflect biological importance.

To examine the localization of the PSEN1 and PSEN2 proteins in situ we utilized immunohistochemical stainings at embryonic day 100 brain slides with antibodies for PSEN1 and PSEN2. PSEN1 staining was more intense and diffusible outside cell bodies than observed for the PSEN2 staining (FIG. 31). We note that all PSEN2 stained regions also were positive for PSEN1 staining (FIG. 31). No clear alterations in localization or intensity of PSEN1 and PSEN2 staining were detected in analysis of other embryonic time points or brain regions (data not shown). Intracellular immunostaining was confined to the cytoplasm with a distinct sparing of the nuclei. The immunostaining was observed in all parts of the CNS, especially in neurons but also to some extent in astrocytes (FIG. 31 and data not shown). In cortex both pyramidal and nonpyramidal cells were stained (FIG. 31). Also all hippocampus CA subfields and the granule cells were PSEN positive (FIG. 31). The immunohistochemical analysis supports that the PSEN proteins are located in the majority, if not all, of the neurons. Moreover, all PSEN2 stained cell types were also positive for PSEN1 staining in accordance with the observed redundancies in PSEN1 and PSEN2 functions [63,64].

TABLE 9

| Genotype-frequencies of a C/T SNP in position 1163 (DQ86246) in PSEN1 intron 8 in a pig breed-panel. |                |                      |      |      |
|------------------------------------------------------------------------------------------------------|----------------|----------------------|------|------|
| Breed                                                                                                | No. of animals | Genotype frequencies |      |      |
|                                                                                                      |                | SNP position 1163    |      |      |
|                                                                                                      |                | C/C                  | T/T  | C/T  |
| Landrace                                                                                             | 14             | 0                    | 0.71 | 0.29 |
| Duroc                                                                                                | 15             | 0                    | 0.60 | 0.40 |
| Hampshire                                                                                            | 17             | 1                    | 0    | 0    |
| Yorkshire                                                                                            | 14             | 0                    | 0.62 | 0.38 |

TABLE 10

| Genotype-frequencies for three SNPs in PSEN1 intron 10 (DQ86246) in a pig breed-panel. |                |                        |      |      |                   |     |      |
|----------------------------------------------------------------------------------------|----------------|------------------------|------|------|-------------------|-----|------|
| Breed                                                                                  | No. of animals | Genotype frequencies   |      |      |                   |     |      |
|                                                                                        |                | SNP position 1535/1575 |      |      | SNP position 1600 |     |      |
|                                                                                        |                | C/C                    | T/T  | C/T  | G/G               | A/A | G/A  |
| Landrace                                                                               | 14             | 0.71                   | 0    | 0.29 | 1                 | 0   | 0    |
| Duroc                                                                                  | 14             | 0.57                   | 0.07 | 0.36 | 1                 | 0   | 0    |
| Hampshire                                                                              | 11             | 0                      | 1    | 0    | 1                 | 0   | 0    |
| Yorkshire                                                                              | 16             | 0.63                   | 0    | 0.37 | 0.69              | 0   | 0.31 |

Example 4

Model Animal of Diseases Related to Trinucleotide Repeat Sequences

Human TNR disease causing regions are in most cases also identifiable in the primate and rodent genomes [65-67]. However, in rodents the TNR regions in general are composed of significantly fewer TNR units and are less polymorphic. As TNR sequences are rapidly evolving and may functionally influence the affected genes, changes in such regions have the potential to participate in functional diversification [65, 68]. To analyse how the disease causing TNR regions identified in humans have evolved in the porcine genome, we analysed porcine TNRs. We here describe that in terms of TNR tract lengths the porcine TNRs in general represent an intermediate between rodent and humans and that several of the TNRs are polymorphic in the pig. In addition, the length of TNRs was in several of the porcine loci comparable to the lengths normally identified in primates.

Genomic Samples

Genomic DNA was prepared from unrelated (no common parents and grandparents) Duroc, Landrace, Hampshire, Yorkshire, and Goettingen minipig males according to standard procedures. The DNA was isolated from EDTA stabilized blood using a salting out procedure [69].

PCR and Sequencing of Genomic DNA

To sequence porcine genomic TNR regions flanking sequences conserved between mouse and humans were identified and corresponding PCR primers designed. 50 ng of Duroc pig genomic DNA was used in PCR with conditions 95° C. 30", 58° C. 30", 72° C. 1', cycles. Standard taq polymerase PCR conditions were used except for the inclusion of 1 M Betaine and 5% DMSO. After agarose gel electrophoresis analysis DNA of expected size was purified and sequenced. If the intensity of bands or the sequencing result was evaluated inadequate for further analysis new PCR prim-

ers were designed either based on the evolutionary approach or nested according to determined sequences. By this scheme the following optimized primer sets were used to amplify genomic TNR regions (all PCR reactions run for 35 cycles with 50 ng genomic DNA as input): SCA1: SCA1+, CAGCGCTCCCAGCTGGAGG (SEQ ID NO: 127); SCA1-, GGAYGTACTGGTTCTGCTGG (SEQ ID NO:128); 95° C. 30", 58° C. 30", 72° C. 1' with betaine and DMSO. SCA2: SCA2NyTRI-, GCCACCGTAGAGGAG-GAGGAAG (SEQ ID NO:129); SCA2TRI(+), CTCACCAT-GTCGCTGAAGC (SEQ ID NO:130); 95° C. 30", 58° C. 30", 72° C. 1' with betaine and DMSO. SCA3: SCA3-I7+, CCATGGGAATAGTTTTTCTCATG (SEQ ID NO:131); SCA3exon10(-), GGTTGGCTTTTCACATGGATGTG (SEQ ID NO:132); 95° C. 30", 58° C. 30", 72° C. 1' with betaine and DMSO. SCA6: SCA6nyTRI+, CGGCCA-CACGTGTCCTATTC (SEQ ID NO:133); SCA6NYTRI-, GGCCGCTGGGGGCCGCTCG (SEQ ID NO:134); 95° C. 30", 58° C. 30", 72° C. 1' with betaine and DMSO. SCA7: SCA7Tri(+), GGAGCGGAAAGAATGTCGGAG (SEQ ID NO:135); SCA7Tri(-), CCCACAGATTCCACGACTGTC (SEQ ID NO:136); 95° C. 30", 58° C. 30", 72° C. 1' with betaine and DMSO. SCA17: pTBP-, GAAGAGCTGTG-GAGTCTGG (SEQ ID NO:137); pTBP+, CTATC-CATTTTGGAGGAGCAG (SEQ ID NO:138); 95° C. 30", 58° C. 30", 72° C. 1' with betaine and DMSO. DRPLA: Drpla-Ny+, GGAGGCCAGTCCACTGCTCAC (SEQ ID NO:139); Drpla-Ny-, GGGAGACATGGCATAAGGGTG (SEQ ID NO:79); 95° C. 30", 58° C. 30", 72° C. 1' with betaine and DMSO. SMBA: ARTri+, X; ARTri-, X, 94° C. 45", 58° C. 30", 72° C. 2'. HD: pHUNNYRE+, CCGCCATG-GCGACCCTGGAAA (SEQ ID NO:140); pHUNNYRE-, GGTGGCGGCTGAGGAGGCTG (SEQ ID NO:141); 95° C. 30", 65° C. 30", 72° C. 1' with betaine and DMSO. FMR1: FMR1(Ny+1), CGTTTCGGTTTCACTTCCGGTG (SEQ ID NO:142); FMR1Zoo-, CCGCACTTCCACCAC-CAGCTC (SEQ ID NO:143); 95° C. 30", 60° C. 30", 72° C. 1' with betaine and DMSO. FMR2: FMR2-Ny-, TGCGGCG-GCAGCAGCCGCTAC (SEQ ID NO:144); FMR2(Ny+2), CCCCTGTGAGTGTGTAAGTGTG (SEQ ID NO:145); 95° C. 30", 58° C. 30", 72° C. 1' with betaine and DMSO. SCA12: SCA12TRI(+), GGGAGGAGCCTCGCCTTTAATG (SEQ ID NO:146); SCA12TRI(-), CGCGACAAAATGGTGC-CTTTC (SEQ ID NO:147), 95° C. 30", 58° C., 30", 72° C. 1' with betaine and DMSO. DMPK: gDMPKpoly+, GCCCT-GCTGCCTTCTCTAGGTC (SEQ ID NO:148); gDMPK-poly-, CCCCAGCTCTAGCCCTGTGATC (SEQ ID NO:149), 94° C. 30", 64° C. 30", 72° C. 2'. DNA fragments were purified from agarose gels using GFX columns (Amersham Biosciences) and sequenced according to standard procedures. DNA fragments were amplified from Duroc, Landrace, Hampshire, Yorkshire, and Goettingen minipig male genomic DNA.

Sequence information for TNRs in *Homo sapiens* (human), *Pan troglodytes* (chimpanzee), *Canis familiaris* (dog), *Rattus norvegicus* (rat), *Mus musculus* (mouse), and *Monodelphis domestica* (opossum) was extracted from genome browsers at NCBI ([www.ncbi.nlm.nih.gov/Genomes](http://www.ncbi.nlm.nih.gov/Genomes)).

Microsatellite Analysis on Sows and Offspring Originating from Boars with Extended TNRs

Genotyping of different Huntingtin allele lengths was performed by microsatellite analysis in a porcine material consisting of 14 Duroc boars, 611 Landrace and Landrace×Yorkshire crossbred sows and 349 offspring originating from 4 of the Duroc boars and the aforementioned sows. The following primers were used; Fw: FAM-CCGCCATGGCGACCCTG-GAAA (SEQ ID NO:150), Rw: GGTGGCGGCTGAGGAG-

GCTG (SEQ ID NO:151). The amplicon was amplified in a total volume of 10 µL in a mixture consisting of: 50 ng of genomic DNA, 5 pmol of each primer, 2.5 mM dNTPs, 1 µL of 10x reaction buffer, 0.5 µL DMSO, 2.5 µL 4 M Betaine, and 5 U Taq DNA polymerase (Applied Biosystems, USA). PCR amplification was as follows: initial denaturation for 4 min at 95° C., and 35 cycles at 95° C. for 30 sec, 64° C. for 30 sec, 72° C. for 1 min. An extension step of 72° C. for 5 min was added after the final cycle. PCR products were denatured with formamide and electrophoresis was carried out on a 3730 DNA Analyzer (Applied Biosystems, USA) using the recommended protocol. Size analyses of DNA fragments were accomplished with the GeneMapper® Software Ver 3.0 (Applied Biosystems, USA). The internal size standard GeneScan-LIZ 500 (Applied Biosystems, USA) was employed for allele sizing.

#### Accession numbers

The determined porcine TNR regions and flanking sequences were submitted to genebank and have been assigned the following accession numbers: SCA1 (DQ915251, DQ915252), SCA2 (DQ915254), SCA3 (DQ915255, DQ915256), SCA6 (DQ915259, DQ915260, DQ915261), SCA7 (DQ915262), SCA17 (DQ915258), DRPLA (DQ915263, DQ915264), SMBA (DQ915257), HD (DQ915274, DQ915275, DQ915276, DQ915277, DQ915278, DQ915279, DQ915280, DQ915281, DQ915282), FMR1 (DQ915269, DQ915270, DQ915271, DQ915272, DQ915273), FMR2 (DQ915268), SCA12 (DQ915265, DQ915266, DQ915267), DMPK (DQ915253). Results

To sequence porcine genomic regions homologous to human disease causing TNRs we first identified flanking sequences showing highly conserved regions between mouse and humans. Employing this PCR approach 12 porcine genomic loci corresponding to human disease causing TNRs were amplified. The identified TNRs were located in coding regions and 5'-UTRs. The DMPK 3'-UTR TNR was amplified using primers based on EST sequences available in Genbank. To search for TNR polymorphisms in different porcine breeds we included Duroc, Landrace, Hampshire, Yorkshire and Goettingen minipig. For each of the pig breeds a number of animals were analysed assuring the detection of common alleles (allele frequency >10%).

Porcine genomic sequences homologous to human non-coding TNR expansion regions. We first addressed porcine genomic sequences homologous to human non-coding TNRs.

DMPK: In the 3'-UTR of the human myotonic dystrophy protein kinase gene, DMPK, a CTG TNR is located [19-23]. The normal size of this TNR varies between 5 and 37. Expansions from above 50 to several thousand CTG repeats result in myotonic dystrophy. A CTG TNR consisting of 4 CTG repeats in all the pig breeds studied (Duroc, Landrace, Yorkshire, Hampshire, and minipigs) (FIG. 32) was identified at the same localization in the porcine DMPK. No length variation in the DMPK TNR was identified (FIG. 32). The repeat number found is below the minimum number of CTG repeats (5 CTGs) observed in humans. In the mouse the TNR sequence of DMPK is composed of 2 CAG repeats flanked by single CTG repeats (FIG. 32). In dog and rat a single CTG is present flanked by other types of TNRs (FIG. 32).

SCA12: The SCA12 CAG TNR within the 5'-UTR of the human PPP2R2B gene normally varies in size from 7 to 28 repeats and in the expanded form from above 65 to 78 TNRs [27]. Three alleles consisting of 8, 9, and 10 CAG repeats were identified in the porcine breeds (FIG. 32). The most abundant allele in Duroc contained 8 CAG repeats, whereas

the most abundant allele in Hampshire contained 10 CAG repeats (FIG. 32). An allele containing 9 CAG repeats was the only allele observed in Landrace, Yorkshire and Minipigs (FIG. 32). The presence of long uninterrupted CAG TNRs in the porcine SCA12 locus is distinct from the mouse and rat SCA12 locus which is composed of CAG TNRs interrupted with CAC and GAG triplets (FIG. 32). Notably, the lengths of the porcine SCA12 alleles are comparable and even higher than SCA12 allele lengths identified in some humans (FIG. 32).

FMR1/FRAXA: In the promoter region of the human FMR1 gene, 6 to 52 CGG repeats are normally present [24, 25]. Expansions in the range of 55 to 200 repeats result in the pre-mutation while the full mutation ranges from 200 to several thousand repeats resulting in fragile X syndrome. The sequence of the FMR1 TNR region in Duroc showed the presence of two alleles: a 14 CGG repeat allele with a frequency of 90% and a 13 CGG repeat allele with a frequency of 10% (FIG. 32). Sequence analysis of the FMR1 TNR in the other porcine breeds showed a high degree of FMR1 TNR length polymorphisms. A 15 CGG repeat allele was identified in Duroc, Hampshire and Yorkshire (FIG. 32). This allele was the most common in Yorkshire, whereas a 9 CAG repeat allele was also identified in Hampshire and a 12 CAG repeat allele in Duroc and Minipigs. No allele polymorphism was observed in Landrace. All the porcine FMR1 alleles were longer than the homologous mouse TNR sequence which is composed of 6 CGG repeats and 2 CGG repeats separated by a CGA (FIG. 32). The dog FMR1 TNR has a size similar to the pig TNR (FIG. 32). In the most common type of human FMR1 TNR allele two groups of CGG repeats are separated by an AGG triplet (FIG. 32). Also the chimpanzee FMR1 TNR is highly polymorphic and includes AGG triplet interruptions [70]. Interestingly, the porcine FMR1 TNR length exceeds the minimal length present in the human FMR1 CGG TNR prone to expand.

FMR2/FRAXE: The number of CCG repeats in the TNR of the 5' end of the human FMR2 gene varies from 6 to 35 [26]. Expansions containing from 61 to 200 repeats result in the pre-mutation and expansions above 200 repeats result in the full mutation and the fragile X syndrome. The homologous region in the porcine FMR2 gene was found to contain 7 CCG repeats in all breeds analysed (FIG. 32). The porcine TNR length exceeds the length of the homologous mouse TNR which is composed of 4 CCG repeats (FIG. 32). Furthermore, the length of the porcine CCG TNR is longer than the minimal CCG allele length identified in humans (FIG. 32).

Porcine Genomic Sequences Homologous to Human Poly-Glutamine Coding TNR Expansion Regions.

Next we addressed the sequence of poly-glutamine coding TNR sequences of nine porcine loci. SCA1: In the human SCA1 locus CAG TNR expansions in the ATX1 protein causes spinocerebellar ataxia [71, 73]. The human SCA1 TNR region is characterized by the presence of 12 CAG repeats followed by two CAT repeats flanking a CAG triplet [28]. The CAG TNR prone to expand is normally composed of between 6 and 39 repeats and the expanded version consists of 41 to 81 repeats. The porcine SCA1 TNR is composed of two CAG repeats separated by eight proline encoding triplets (FIG. 33). However, in Minipigs a variant was detected; the most common allele having a CAG TNR duplication (FIG. 33). The dog SCA1 region includes 6 CAG repeats (FIG. 33). The mouse and rat homologous region is composed of two CAG repeats and three proline coding triplets (FIG. 33). Thus, in terms of CAG repeat numbers the porcine and rodent SCA1 TNRs are similar but distinct from the homologous human TNR (FIG. 33). However, due to the

presence of numerous proline codons (CCX) the porcine SCA1 TNR have increased complexity compared to the TNR in rodents.

SCA2: The SCA2 TNR expansion, affecting the ATX2 protein, results in spinocerebellar ataxia [73]. This TNR normally consists of 15 to 30 CAG repeats and the expanded form ranges from 35 to 59 triplets [29]. The porcine locus is composed of 7 CAG repeats separated by two CAA triplets (FIG. 33). Accordingly, the region encodes a stretch of nine poly-glutamines. No polymorphism whatsoever was observed in the porcine SCA2 TNR region. The dog SCA2 TNR had proline interruptions in the poly-glutamine stretch (FIG. 33). The homologous rodent SCA2 TNR is composed of CAG repeats separated by a proline encoding triplet (FIG. 33).

SCA3: In the human SCA3 locus a CAG TNR expansion in the ataxin-3 gene above 54 repeats results in ataxia whereas the normal number of CAG repeats varies between 12 and 36 [30-32]. In pigs a five CAG TNR allele was identified in Duroc, Hampshire, and Landrace whereas five and six CAG TNR alleles were identified in Yorkshire and Minipigs (FIG. 33). In terms of the number of encoded poly-glutamines the porcine SCA3 TNR region is homologous to the mouse SCA3 TNR region (FIG. 33) and well below the critical number in the human counterpart. The dog SCA3 TNR encodes 12 glutamines but includes several CAA interrupting triplets (FIG. 33).

SCA6: The SCA6 TNR expansion in the CACNA1A voltage dependent calcium channel results in ataxia [33]. The normal number of TNRs is between 4 and 18 and expansions from 21 to 27 TNRs are disease causative. In pigs a SCA6 allele was identified composed of 5 and 4 CAG repeats separated by a CAA triplet thereby encoding a poly-glutamine stretch of 10 (FIG. 33). In Minipigs longer SCA6 alleles composed of 7 or 9 CAG repeats followed by the CAA triplet and 4 CAG repeats (FIG. 33) were identified. These alleles encode stretches of 12 and 14 poly-glutamines, respectively. The poly-glutamine stretches encoded by the porcine SCA6 TNR region were comparable in length to the normal range encoded by the human SCA6 sequence, and the 14 poly-glutamine stretch identified in Minipigs matches the upper range of the more common human alleles (FIG. 33). In dog a 10 CAG SCA6 TNR was present (FIG. 33). We note the absence of a SCA6 TNR in rodents and a high degree of divergence in the CACNA1A sequence between rodents and pig, dog, and primates at the particular genomic position.

SCA7: The TNR of the human SCA7 locus in the N-terminal end of the ataxin-7 protein is normally composed of 7 to 35 CAG repeats [54]. Disease causing expansions range from 37 to 200 repeats. The TNR of the porcine SCA7 locus contains 5 CAG repeats and no polymorphisms were observed in the breeds (FIG. 33). Similarly, the TNR of the mouse SCA7 locus contains 5 CAG repeats (FIG. 33). Interestingly, a SCA7 allele with 5 CAG repeats has also been identified in humans. Note that the SCA7 CAG repeats are flanked by a poly-alanine stretch and a glutamine and proline rich stretch highly variable between the examined mammalian genomes (data not shown).

DRPLA: CAG expansions within the human atrophin-1 gene results in dentatorubral-pallidoluysian atrophy (DRPLA) [36]. The normal range of repetitive CAG repeats is from 3 to 25, and in patients with DRPLA allele sizes have expanded to 49 to 88 CAG repeats. The most common natural occurring human allele encodes a stretch of 17 poly-glutamines. In the porcine atrophin-1 TNR, six CAG repeats flanked by multiple CAG and CAA triplets resulting in an allele encoding 14 poly-glutamines (FIG. 33) was identified. Moreover, in Minipigs an allele with seven CAGs resulting in a 15 poly-glutamine encoding allele was observed (FIG. 33). This means that the length of the porcine atrophin-1 poly-

glutamine stretches is above the minimal length observed in humans. The TNR of the mouse atrophin-1 gene encodes six glutamines with an interrupting proline and from the rat gene is encoded 11 glutamines highly interrupted by proline residues (FIG. 33). The dog atrophin-1 TNR encodes a stretch of 12 poly-glutamines (FIG. 33). In mammals the atrophin-1 TNR is flanked by histidine rich stretches polymorphic between the examined mammalian genomes (data not shown).

SCA17: A CAG expansion in the TATA box binding protein (TBP) gene is causative of the SCA17 phenotype resulting in ataxia [35]. The human TNR region is composed of two groups of CAG repeats separated by multiple CAA and CAG triplets. Expansions normally progress from the larger of the two CAG groups. The normal stretch of encoded poly-glutamines varies between 29 and 42 whereas poly-glutamine stretches from 47 to 55 have been identified in SCA17 patients. The porcine SCA17 TNR region encodes 26 poly-glutamines and thus is the largest poly-glutamine encoding TNR identified in pigs (FIG. 33). The pig SCA17 sequence is composed of four groups of CAG TNRs intervened by CAA triplets (FIG. 33). The longest CAG group consists of 10 CAGs. No allele polymorphism was identified in porcine SCA17. In comparison, mouse SCA17 TNR encodes 13 poly-glutamines and a maximum of three CAG triplets in one stretch (FIG. 33). The dog SCA17 TNR encodes 22 glutamines but includes several alanine interruptions (FIG. 33).

SBMA: CAG repeat expansions in exon 1 of the androgen receptor (AR) gene on the X-chromosome results in spinal and bulbar muscular atrophy (Kennedy's disease) [37]. The normal length of the human CAG TNR is between 11 and 33 CAG copies and in diseased individuals the expansion ranges from 38 to 62. In the pig an AR allele encoding 7 poly-glutamines interrupted by a single CTG leucine triplet was identified (FIG. 33). No TNR variation was observed between the different porcine breeds. In mouse and rat the AR TNR sequence encodes 3 glutamines interrupted by a single AGG arginine triplet or CGG arginine triplet, respectively (FIG. 33). The dog AR TNR is composed of a 10 CAG repeats (FIG. 33). Note, in mammals the TNR is flanked by a proline and glutamine rich stretch highly polymorphic between the examined mammalian genomes (data not shown).

HD: The CAG TNR in the Huntingtin gene is located in the 5'-end of the coding region. Normally, the gene contains from 6 to 35 CAG repeats and in Huntington's disease patients more than 35 CAG repeats are present [74]. A large degree of variation was observed in the pig Huntingtin TNR region (FIG. 33). This difference was due both to a variable number of CAG repeats but also due to the absence or presence of a CAA triplet which separates the continuous CAG theme into two groups (FIG. 33). Alleles with sizes encoding 13 to 24 poly-glutamines from were identified. Highly interesting, in Duroc, an allele composed of a stretch of 21 uninterrupted CAGs, a CAA triplet, and two CAGs resulting in the encoding of a total of 24 poly-glutamines (FIG. 33) was identified. This allele represents the largest number of uninterrupted CAGs identified in the analysis of porcine TNRs. The long allele was specifically identified in Duroc and has an allele frequency of 20%. The Minipig Huntingtin gene and polymorphisms therein were described previously [75]. The numbers of poly-glutamines encoded by porcine Huntingtin TNRs are indeed comparable to the human repeat and are for the 24 poly-glutamine allele even above the number of poly-glutamines most frequently found in human Huntingtin alleles. In contrast the mouse Huntingtin TNR region encodes seven poly-glutamines intervened by a CAA triplet and the dog TNR region 10 poly-glutamines (FIG. 33). The Huntingtin TNR is

flanked by a proline and glutamine rich stretch polymorphic between the examined mammalian genomes (data not shown).

The porcine Huntingtin TNR length is meiotic stable

Since a long uninterrupted CAG TNR sequence was present in the Huntingtin gene of Duroc pigs, we next examined if this sequence was stably inherited or prone to retractions or expansions. For this purpose we used a porcine material consisting of Duroc boars crossed with Landrace and Landrace/Yorkshire crossbreed sows. The genotyping of different Huntingtin allele lengths was performed by microsatellite analysis. From the boar cohort, four heterozygous boars were identified having both a 161 bp fragment and a 140 bp fragment corresponding to 24 and 17 glutamines, respectively. The genotyping result of the 4 heterozygous boars was verified by DNA sequencing. The genotyping data from the cohort of the 611 sows used in the breeding scheme resulted in the identification of the alleles also present in the pure Landrace and Yorkshire breeds. Furthermore, two new Huntingtin alleles encoding 14 and 15 glutamines not present in the pure breeds were identified in the sow cohort (table 11). Also the 24 poly-glutamine encoding allele was present in the sow population, however only at a low frequency (0.3%, table 11). Interestingly, no alleles were identified with a size less than 13 poly-glutamines or a polyglutamine number of 19, 20, 21, 22, or 23 (table 1 and data not shown). However, since the population of sows was not completely unrelated, the allele frequency calculations are only indicative. The group of genotyped offspring consisted of 349 pigs. All these 349 animals had a genotype in accordance with the inheritance of a maternal and paternal Huntingtin allele without any TNR retractions or expansions (table 12). Thus, we could not identify any evidence for transmission instability of Huntingtin TNRs.

TABLE 11

| Meiotic stability of porcine Huntingtin (CAG)24 and (CAG)17 alleles. |                               |                                      |                                     |                                      |                                     |                                       |                                      |                                     |
|----------------------------------------------------------------------|-------------------------------|--------------------------------------|-------------------------------------|--------------------------------------|-------------------------------------|---------------------------------------|--------------------------------------|-------------------------------------|
| Female haplotypes                                                    |                               |                                      |                                     |                                      |                                     |                                       |                                      |                                     |
|                                                                      | Q = 13<br>L = 128<br>F = 0.18 | Q = 14<br>L = 131<br>F = 0.02        | Q = 15<br>L = 134<br>F = 0.05       | Q = 16<br>L = 137<br>F = 0.025       | Q = 17<br>L = 140<br>F = 0.51       | Q = 18<br>L = 143<br>F = 0.21         | Q = 24<br>L = 161<br>F = 0.003       |                                     |
| Male<br>haplotypes                                                   | Q = 17<br>L = 140             | Q = 13, 17<br>L = 128, 140<br>N = 24 | Q = 14, 17<br>L = 131, 140<br>N = 0 | Q = 15, 17<br>L = 134, 140<br>N = 11 | Q = 16, 17<br>L = 137, 140<br>N = 2 | Q = 17, 17<br>L = 140, 140<br>N = 88  | Q = 18, 17<br>L = 143, 140<br>N = 49 | Q = 24, 17<br>L = 161, 140<br>N = 0 |
|                                                                      | Q = 24<br>L = 161             | Q = 13, 24<br>L = 128, 161<br>N = 18 | Q = 14, 24<br>L = 131, 161<br>N = 0 | Q = 15, 24<br>L = 134, 161<br>N = 10 | Q = 16, 24<br>L = 137, 161<br>N = 1 | Q = 17, 24<br>L = 140, 161<br>N = 115 | Q = 18, 24<br>L = 143, 161<br>N = 31 | Q = 24, 24<br>L = 161, 161<br>N = 0 |
|                                                                      |                               |                                      |                                     |                                      |                                     |                                       |                                      |                                     |
|                                                                      |                               |                                      |                                     |                                      |                                     |                                       |                                      |                                     |

The paternal genotype was 140/161. The sow haplotypes are indicated together with the frequency (F) within the breeding cohort. For all offspring a genotype could be assigned in accordance with transmission of both paternal and maternal alleles not subjected to expansions or retractions. A total of 349 offspring were genotyped. The genotypes are visualized according to the length (L) of the analysed fragments. Q indicates the number of glutamines encoded from the TNR alleles. N indicates the number of offspring with the indicated genotype.

Example 5

Animal Model of Chondrodysplasia

Only a very limited amount of knowledge is available regarding the presence of collagen X in permanent cartilages,

such as trachea, in comparison to growth plate cartilages. We isolated the full length cDNA encoding collagen X from porcine trachea illustrating that collagen X is not solely present in hypotrophic chondrocytes of calcifying matrix typically present in long bones. However, in humans collagen X have, previously been shown in trachea especially in elderly individuals where ossification occur in the tracheal cartilage as a result of the progressing age. Furthermore, in developing rat tracheal cartilage, collagen X was confined to the peripheral uncalcified region of the cartilage [76] indicating that collagen X might play a role beside providing the molecular structural environment in relation to endochondral ossification, however this is not confirmed in humans [77].

Materials and Methods  
RNA Isolation

The pig trachea tissue used for RT-PCR cloning of COLA was obtained from an adult pig. Tissue was dissected and pulverized in liquid nitrogen after removal. Total RNA was isolated by RNeasy method (Qiagen). The integrity of RNA samples was verified by ethidium bromide staining of the ribosomal RNA on 1.5% agarose gels.

DNA Constructs

Generation of a porcine COL10A1 clone was accomplished in the following way: RNA derived from adult porcine trachea was employed in a cDNA synthesis using conditions where 5 µg of total RNA was mixed with 1 µL of oligo (dT) 12-18 (500 µg/mL), and DEPC treated H<sub>2</sub>O to a final volume of 12 µL. The mixture was incubated at 70° C. for 10 min, after which 4 µL of 5× first-strand buffer, 2 µL of 0.1 mM DTT, 1 µL of 10 mM dNTP mix and 1 µL (200 U/µL) of Superscript II (Invitrogen) was added and the sample was further incubated at 42° C. for 1 hour followed by an inactivation step at 70° C. for 15 min. oligonucleotides used for

RT-PCR cloning were derived from the genomic COL10A1 sequence (Accession number: AF222861) and also contained linkers (Bgl II in the sense primer and Eco RI in the antisense primer) for subsequent cloning. The RT-PCR reaction mix contained 2.5 µL cDNA, 1.5 mM MgCl<sub>2</sub>, 0.2 mM dNTP, 10 pmol of each primer (COL-F: 5'-AACAGATCTATGCTGC-CACAAACAGCCCTTTTGCT-3' (SEQ ID NO:152) and COL-R: 5'-GCAGAATTCTCACATTGGAGCCACTAG-GAATCCT-3' (SEQ ID NO:153), and 1.0 U Phusion Fidelity DNA polymerase (Finnzymes), in a total volume of 25 µL using the following conditions: denaturation at 98° C. for 2 min., followed by 30 cycles of 98° C. for 10 s., 60° C. for 30 s., and 72° C. for 1 min. The PCR program was concluded by a final extension step at 72° C. for 5 min. The PCR was accomplished in a GeneAmp® PCR System 9700 (Applied Biosystems). The amplification product was applied to a 1% ethidium bromide stained agarose gel and a fluorescent band

of approximately 2000 bp was isolated using standard procedures and cloned into the pCR®2.1-TOPO vector (Invitrogen, CA) and sequenced in both forward and reverse direction applying standard procedures to ensure that they harboured the COL10A1 amplicon. The COL10A1 plasmid DNA was digested with Eco RI and ligated into a pHCMV1 (Gene Therapy Systems Inc.) expression vector pre-digested with Eco RI. The successful cloning of COL10A1 into the pHCMV1 vector was confirmed by sequencing.

In order to create DNA for incubation of sperm cells, large scale PCR reactions were performed. The PCR reactions were carried out in a GeneAmp® PCR System 9700 (Applied Biosystems) in a final volume of 25 µL consisting of 5 µL 5× Phusion HF buffer, 2 µL dNTP (2.5 mM each) 0.63 µL forward and reverse primer 5 pmol, 0.1 µL Phusion DNA Polymerase (2 U/µL), 1 µL COL10A1-CMV1 template, and 15.6 µL H<sub>2</sub>O. The PCR reaction consisted of an initial denaturation at 98° C. for 30 sec followed by 30 cycles of denaturation for 10 sec at 98° C., annealing at 74° C. for 30 sec and elongation for 95 sec at 72° C. followed by a final elongation step at 72° C. for 7 min. The following primers were used to amplify the COL10A1 construct plus the flanking CMV promoter, intron/enhancer sequence, and SVpolyA, generating a fragment of approximately 3600 bp.

(SEQ ID NO: 154)  
pHCMVF: 5'-GTCGGAACAGGAGAGCGCACGAGGG-3'

(SEQ ID NO: 155)  
pHCMVR: 5'-GGGTGATGGTTACGTAAGTGGGC-3'

In order to purify the generated PCR product a "High Pure PCR Product Purification Kit" (Roche) was applied. The suppliers' instructions were followed throughout the purification procedure. The PCR purified fragments were sequenced to check for errors in the sequence.

#### Preparation of Sperm and DNA Uptake

First and second semen ejaculate, were collected from 8 different boars yielding 16 semen fractions in total. All fractions of spermatozoa had an initial motility of 90 prior to the washing procedure. Seminal fluid was quickly removed by washing the sperm in Fertilization Buffer (FB) consisting of 56.1 g Glucose, 3.5 g EDTA (2H<sub>2</sub>O), 3.5 g Sodium Citrate (2H<sub>2</sub>O), and 1.1 g sodium bicarbonate dissolved in 1 liter of sterilized water. Furthermore 6 mg/ml BSA (Fraction V, Sigma) was added. Briefly, 5 mL of FB/BSA prewarmed to 37° C. was added to 5 mL of undiluted semen and left for 5 minutes at room temperature. Next, FB/BSA at room temperature was added to 50 ml and centrifuged for 10 minutes at room temperature at 500 g. The supernatant was removed and semen was resuspended in 50 mL FB/BSA at room temperature and further centrifuged at 500 g at 17° C., after which, the supernatant was removed again and the spermatozoa was resuspended in 15 mL of FB/BSA. Next, in order to select the optimal donor cells, the spermatozoa from the different boars were quickly examined under a light microscope. The sperm cells originating from the boar having the highest sperm cell motility after the washing procedure were chosen as vehicles for the subsequent transgenic procedures. Furthermore, the atozoa were counted.

1×10<sup>9</sup> sperm cells from the chosen donor boar were incubated for 100 minutes at 17° C. with the linear COL10A1 DNA fragment in a concentration of 0.4 µg DNA/10<sup>6</sup> spermatozoa in a suspension of 120 mL FB/BSA. The container was inverted every 20 minutes to prevent sedimentation of spermatozoa. Finally, the mixture was incubated 10 minutes at room temperature and employed in artificial insemination of a sow in natural heat.

#### Animals

Semen was collected from trained Danish Landrace boars that had abstained for 2 days. one recipient sow (Danish Landrace×Yorkshire) at approximately 140 kg were selected due to its natural heating period and used for artificial insemination (1×10<sup>9</sup> DNA treated spermatozoa/sow) meeting standard insemination procedures. Insemination was accomplished in the local stable areas at DIAS. The sow was examined for pregnancy 24 and 42 days after insemination, showing that was successfully pregnant. After ended gestation period 6 boar and 6 sow piglets were naturally born and blood samples were withdrawn from the piglets three days after birth in EDTA and serum tubes. Due to economical reasons, 9 animals were sacrificed and hence 2 boars and 1 sow piglet were kept for later investigation. The sow was sacrificed at the age of 7 month since severe phenotypic alterations were present. Animal care and experimental procedures met local, national and European Union Guidelines. DNA and RNA Studies

DNA was prepared from EDTA stabilized blood samples from the 12 piglets. RNA was prepared from snap frozen tissues from the sacrificed sow (heart, kidney, liver, lung, skin, ovary, musculus longissimus dorsi, musculus semimembranosus, and musculus triceps brachii). To avoid any contamination, all DNA and RNA samples were extracted in special clean laboratory facilities under highly stringent experimental conditions using standard protocols. PCR and RT-PCR

To ensure the presence of the transgene, 50 ng of genomic DNA from each animal, isolated from blood samples were amplified using the following primers: pHCMV\_430F: 5'-GTCTCCACCCCATTCGACGTC-3' (SEQ ID NO:156) and pHCMV\_646R: 5'-GGATCGGTCCTCCGGTGTCTTC-3' (SEQ ID NO:157) yielding a fragment of 217 bp using the following sample mix 1 µL 10×MgCl<sub>2</sub> free reaction buffer, 0.4 µL 50 mM MgCl<sub>2</sub>, 10 pmol of each primer, 5 mM dNTP-mix, and 0.5 U Dynazyme Ext DNA polymerase. The reaction was performed in a total volume of 10 µL and accomplished as a touchdown PCR in a GeneAmp® PCR system 9700 (Applied Biosystems) under the following conditions: Initial denaturation at 95° C. for 3 min, denaturation at 95° C. for 30 sec, touchdown from 62° C. to 57° C. with a decrement of 0.5° C. for 20 sec, followed by 1 min of elongation at 72° C. per cycle. Furthermore, 35 cycles of 30 sec denaturation at 95° C., 20 sec of annealing at 57° C., and 1 min of elongation at 72° C. was included together with a final elongation step at 72° C. for 7 min.

#### Southern Blot Analysis

Transgene integration was determined by Southern blot analysis of DNA from musculus longissimus dorsi from the affected sow. 10 µg of genomic DNA from the affected sow and from a wild type pig was digested with Bgl II and double digested with Bgl II and Bam HI, respectively, and separated on a 0.9% agarose gel, blotted to a nylon membrane and probed with [32P]-labelled collagen X NC1 fragment derived from PCR amplification using the following primers NC1\_F: 5'-GCTCTAGAGGTCCACCCACCCGAAGG-3' (SEQ ID NO:158) and NC1\_R: 5'-TCTCTAGATCACATTGGAGC-CACTACGAA-3' (SEQ ID NO:159).

#### Histopathology

From the right foreleg tissues from the growth plates (physis) and metaphyses of femur, ulna and radius were sampled together with the articular areas including the articular-epiphyseal cartilage complex of the shoulder-, elbow-, and carpal joints. From the two hind legs similar tissue samples were collected from the hip and knee joints, i.e. from the femoral and tibial bones. Also the osteo-chondral junction of three ribs was sampled for histology. All tissues were fixed in 10% neutral buffered formalin followed by decalcification in a solution containing 3.3% formaldehyde and 17% formic acid

for 2 weeks. The tissues were processed through graded concentrations of alcohol and xylene, and embedded in paraffin wax blocks. Tissue sections of 4-5 $\mu$  were stained by haematoxylin and eosin (HE), and in selected cases by Van Gieson for collagen and safranin o for cartilage matrix [78,79].

#### Results

#### Sperm Mediated Gene Transfer and Genetically Modified Pigs

In order to establish transgenic pigs which could shed light on the functional role of collagen X a COL10A1 cDNA wild type construct was generated. Interestingly, the porcine COL10A1 cDNA was isolated from trachea using primers generated from the previously known COL10A1 sequence [80]. The cDNA fragment was initially cloned into the pCR $\text{\textcircled{R}}$ 2.1-TOPO vector and subsequently successfully removed to the phCMV1 expression vector facilitating constitutive expression qua the CMV promoter. In order to impede possible truncation of important elements following SMGT, the COL10A1 DNA fragment employed in the transgenic procedure, include additional nucleotides 5' and 3' prime to the CMV promoter and the polyA fragment which, constitutes a fragment of approximately 3600 bp in total, FIG. 34.

Initially, eight Danish Landrace boars were used as sperm donors and the sperm fraction showing the highest motility after the initial washing procedure, introduced to remove seminal fluid, was chosen in the subsequent DNA incubation procedure. After ended gestation period 12 normal looking piglets were naturally born and PCR analysis, of DNA isolated from blood, amplifying a 217 bp DNA fragment, located in the 5'-prime phCMV fragment of the construct, showed that all 12 piglets harboured the transgene, see FIG. 35. However, due to economical reasons only 3 piglets were kept for phenotypical investigations.

#### Phenotypic Description

At the age of approximately 5½ month one of the three transgenic animals, a sow, developed clinical manifestations of lameness. The sow was oppressed in its movements rising from primarily difficulties with the forelegs, had a toddling gait, a curved back, which however could be a compensation for the abnormalities arising from the fore legs. The signs became slightly worse and at the age of approximately seven month the sow would only walk when forced to, and it would immediately bent down on the elbows and walk on these. However, for ethical reasons the sow was sacrificed at this point.

#### Southern Blot Analysis

Southern blot analysis, shown in FIG. 36, performed on tissue from musculus longissimus dorsi from the diseased sow and a normal wild type pig reveals additional bands in the affected pig, when digested with Bgl II and Bam HI in comparison to the control using the entire collagen NC1 domain as a radiolabelled probe. This therefore, led us to conclude that the transgene has become integrated into the genome of the affected pig. Unfortunately, Bgl II did only digest the genomic DNA to a limited degree, and hence no difference is seen regarding additional bands in the undigestion using this enzyme alone (lane 1 and 2).

#### Expression Analysis

Expression of the COL10A1 construct was accomplished by RT-PCR using primers located in COL10A1 exon 2 and COL10A1 exon 3 on total RNA isolated musculus triceps brachii, ovary, kidney, skin, liver, lung, musculus longissimus dorsi, musculus semimembranosus, heart, and liver, spleen, kidney, lung, and heart from a wild type control. The RT-PCR analysis revealed expression of collage X in kidney, lung, and heart in the affected sow, although only very limited amounts of transcript are present in kidney, FIG. 37. However, since the PCR is only qualitative, the judgement of expression levels within the samples should be taken with precaution,

although the same amount of total RNA has been used in the cDNA synthesis. Furthermore, no expression of COL10A1 is present in the wild type control tissues.

#### Histopathology

The articular-epiphyseal area of the humeral trochlea constituting the proximal portion of the elbow joint, revealed severe alterations, see FIG. 38. The cartilage was retained with contents of hypertrophied chondrocytes. Within areas of retained cartilage formation of clefts were regularly seen, and in the depth irregular cavitations filled with fibrinous material were present along with eosinophilic streaks. Moreover, the distal growth plates of both ulna and radius were irregular with localized areas of retained cartilage. Lesions were not present within sections from the ribs, the articular-epiphyseal areas or the growth plates of the hind legs.

Thus in conclusion, the integration and expression of the COL10A1 transgene gave rise to a dyschondroplasia phenotype affecting especially the two fore limbs of a sow. The alterations present in the transgenic sow, resembles osteochondrosis which is known to affect younger animals, and is characterised by similar lesions of the articular-epiphyseal cartilage complex [41] as observed in the forelegs of the present sow.

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## SEQUENCE LISTING

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tggagataat acagcaggct gtaccagtgc aggtcctcac tttaatcctc tatccagaaa 360
acacgggtggg ccaaaggatg aagagaggca tgttgagac ttgggcaatg tgactgctga 420
caaagatggt gtggccgatg tgtctattga agattctgtg atctcactct caggagacca 480
ttgcatcatt ggccgcacac tgggtgtcca tgaaaaagca gatgacttgg gcaaaggagg 540
aaatgaagaa agtacaaaga caggaaacgc tggaagtcgt ttggcttgtg gtgtaattgg 600
gatcgcccaa taaacattcc cttggatgta gtctgaggcc ccttaactca tctgttatcc 660
tgctagctgt agaaatgtat cctgataaac attaaacact gtaatcttaa aagtgttaatt 720
gtgtgacttt ttcagagttg ctttaaagta cctgtagtga gaaactgatt tatgatcact 780
tggaagattt gtatagtttt ataaaactca gttaaatgt ctgtttcaat gacctgtatt 840
ttgccagact taaatcacag atgggtatta aacttgtcag aatttctttg tcattcaagc 900
ctgtgaataa aaaccctgta tggcacttat tatgaggcta ttaaaagaat ccaaattcaa 960
actaaaaaaaa aaaaaaaaaa a 981

```

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<210> SEQ ID NO 2
<211> LENGTH: 154
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

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<400> SEQUENCE: 2

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```

Met Ala Thr Lys Ala Val Cys Val Leu Lys Gly Asp Gly Pro Val Gln
1           5           10          15
Gly Ile Ile Asn Phe Glu Gln Lys Glu Ser Asn Gly Pro Val Lys Val
20          25          30
Trp Gly Ser Ile Lys Gly Leu Thr Glu Gly Leu His Gly Phe His Val
35          40          45
His Glu Phe Gly Asp Asn Thr Ala Gly Cys Thr Ser Ala Gly Pro His
50          55          60
Phe Asn Pro Leu Ser Arg Lys His Gly Gly Pro Lys Asp Glu Glu Arg
65          70          75          80
His Val Gly Asp Leu Gly Asn Val Thr Ala Asp Lys Asp Gly Val Ala
85          90          95
Asp Val Ser Ile Glu Asp Ser Val Ile Ser Leu Ser Gly Asp His Cys
100         105         110
Ile Ile Gly Arg Thr Leu Val Val His Glu Lys Ala Asp Asp Leu Gly
115         120         125
Lys Gly Gly Asn Glu Glu Ser Thr Lys Thr Gly Asn Ala Gly Ser Arg
130         135         140
Leu Ala Cys Gly Val Ile Gly Ile Ala Gln
145         150

```

```

<210> SEQ ID NO 3
<211> LENGTH: 462
<212> TYPE: DNA
<213> ORGANISM: Porcine

```

```

<400> SEQUENCE: 3

```

```

atggcgacga aggccgtgtg tgtgtgaag ggcgacggcc cggtgcaggg caccatctac 60
ttcgagctga agggagagaa gacagtgtta gtaacgggaa ccattaaagg actggctgaa 120
ggtgatcatg gattccatgt ccatcagttt ggagataata cacaaggctg taccagtgca 180

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```

ggctctcact tcaatcctga atccaaaaa catggtgggc caaaggatca agagaggcac 240
gttgagagacc tgggcaatgt gactgctggc aaagatgggtg tggccactgt gtacatcgaa 300
gattctgtga tcgcctctc gggagaccat tccatcattg gccgcacaat ggtgggtccat 360
gaaaaaccag atgacttggg cagaggtgga aatgaagaaa gtacaaagac gggaaatgct 420
ggaagtcgtt tggcctgtgg tgtaattggg atcaccagc aa 462

```

```

<210> SEQ ID NO 4
<211> LENGTH: 153
<212> TYPE: PRT
<213> ORGANISM: Porcine

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```

<400> SEQUENCE: 4

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```

Met Ala Thr Lys Ala Val Cys Val Leu Lys Gly Asp Gly Pro Val Gln
1           5           10           15
Gly Thr Ile Tyr Phe Glu Leu Lys Gly Glu Lys Thr Val Leu Val Thr
20          25          30
Gly Thr Ile Lys Gly Leu Ala Glu Gly Asp His Gly Phe His Val His
35          40          45
Gln Phe Gly Asp Asn Thr Gln Gly Cys Thr Ser Ala Gly Pro His Phe
50          55          60
Asn Pro Glu Ser Lys Lys His Gly Gly Pro Lys Asp Gln Glu Arg His
65          70          75          80
Val Gly Asp Leu Gly Asn Val Thr Ala Gly Lys Asp Gly Val Ala Thr
85          90          95
Val Tyr Ile Glu Asp Ser Val Ile Ala Leu Ser Gly Asp His Ser Ile
100         105         110
Ile Gly Arg Thr Met Val Val His Glu Lys Pro Asp Asp Leu Gly Arg
115         120         125
Gly Gly Asn Glu Glu Ser Thr Lys Thr Gly Asn Ala Gly Ser Arg Leu
130         135         140
Ala Cys Gly Val Ile Gly Ile Thr Gln
145         150

```

```

<210> SEQ ID NO 5
<211> LENGTH: 462
<212> TYPE: DNA
<213> ORGANISM: Porcine

```

```

<400> SEQUENCE: 5

```

```

atggcgacga aggccgtgtg tgtgctgaag ggcgacggcc cgggtgcaggg caccatctac 60
ttcgagctga agggagagaa gacagtgtta gtaacgggaa ccattaaagg actggctgaa 120
ggtgatcatg gattccatgt ccatcagttt ggagataata cacaagctg taccagtgca 180
ggctctcact tcaatcctga atccaaaaa catggtgggc caaaggatca agagaggcac 240
gttgagagacc tgggcaatgt gactgctggc aaagatcgtg tggccactgt gtacatcgaa 300
gattctgtga tcgcctctc gggagaccat tccatcattg gccgcacaat ggtgggtccat 360
gaaaaaccag atgacttggg cagaggtgga aatgaagaaa gtacaaagac gggaaatgct 420
ggaagtcgtt tggcctgtgg tgtaattggg atcaccagc aa 462

```

```

<210> SEQ ID NO 6
<211> LENGTH: 153
<212> TYPE: PRT
<213> ORGANISM: Porcine

```

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<400> SEQUENCE: 6

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Met Ala Thr Lys Ala Val Cys Val Leu Lys Gly Asp Gly Pro Val Gln  
 1 5 10 15  
 Gly Thr Ile Tyr Phe Glu Leu Lys Gly Glu Lys Thr Val Leu Val Thr  
 20 25 30  
 Gly Thr Ile Lys Gly Leu Ala Glu Gly Asp His Gly Phe His Val His  
 35 40 45  
 Gln Phe Gly Asp Asn Thr Gln Gly Cys Thr Ser Ala Gly Pro His Phe  
 50 55 60  
 Asn Pro Glu Ser Lys Lys His Gly Gly Pro Lys Asp Gln Glu Arg His  
 65 70 75 80  
 Val Gly Asp Leu Gly Asn Val Thr Ala Gly Lys Asp Arg Val Ala Thr  
 85 90 95  
 Val Tyr Ile Glu Asp Ser Val Ile Ala Leu Ser Gly Asp His Ser Ile  
 100 105 110  
 Ile Gly Arg Thr Met Val Val His Glu Lys Pro Asp Asp Leu Gly Arg  
 115 120 125  
 Gly Gly Asn Glu Glu Ser Thr Lys Thr Gly Asn Ala Gly Ser Arg Leu  
 130 135 140  
 Ala Cys Gly Val Ile Gly Ile Thr Gln  
 145 150

&lt;210&gt; SEQ ID NO 7

&lt;211&gt; LENGTH: 2763

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Homo Sapiens

&lt;400&gt; SEQUENCE: 7

|                                                                    |      |
|--------------------------------------------------------------------|------|
| tgggacaggc agctccgggg tccgcggttt cacatcggaa acaaaacagc ggctggtctg  | 60   |
| gaaggaacct gagctacgag ccgcggcgcc agcggggcgg cggggaagcg tataccta    | 120  |
| ctgggagcct gcaagtacac acagcctttg cggtccttag acagcttggc ctggaggaga  | 180  |
| acacatgaaa gaaagaacct caagaggctt tgttttctgt gaaacagtat ttctatacag  | 240  |
| ttgtccaat gacagagtta cctgcaccgt tgtcctactt ccagaatgca cagatgtctg   | 300  |
| aggacaacca cctgagcaat actgtacgta gccagaatga caatagagaa cggcaggagc  | 360  |
| acaacgacag acggagcctt ggccaccctg agccattatc taatggacga ccccagggtg  | 420  |
| actcccggca ggtggtggag caagatgagg aagaagatga ggagctgaca ttgaaatatg  | 480  |
| gcgccaagca tgtgatcatg ctctttgtcc ctgtgactct ctgcatggcg gtggtcgtgg  | 540  |
| ctaccattaa gtcagtcagc ttttataccc ggaaggatgg gcagctaata tatacccat   | 600  |
| tcacagaaga taccgagact gtgggccaga gagccctgca ctcaattctg aatgctgcca  | 660  |
| tcatgatcag tgtcattgtt gtcatgacta tcctcctggg ggttctgtat aaatacaggt  | 720  |
| gctataaggt catccatgcc tggcttatta tatcatctct attgttgctg ttcttttttt  | 780  |
| cattcattta cttgggggaa gtgtttaaaa cctataacgt tgctgtggac tacattactg  | 840  |
| ttgcactcct gatctggaat tttggtgtgg tgggaatgat ttccattcac tggaaaggtc  | 900  |
| cacttcgact ccagcaggca tatctcatta tgattagtgc cctcatggcc ctgggtgttta | 960  |
| tcaagtacct ccctgaatgg actgcgtggc tcatcttggc tgtgatttca gtatatgatt  | 1020 |
| tagtggtgtg tttgtgtccg aaagggtccac ttcgtatgct ggttgaacaa gctcaggaga | 1080 |
| gaaatgaaac gctttttcca gctctcattt actcctcaac aatgggtgtg ttgggtgaata | 1140 |
| tggcagaagg agaccgggaa gctcaaagga gaggatccaa aaattccaag tataatgcag  | 1200 |
| aaagcacaga aagggagtca caagacactg ttgcagagaa tgatgatggc gggttcagtg  | 1260 |

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aggaatggga agcccagagg gacagtcato tagggcctca tcgctctaca cctgagtcac 1320
gagctgctgt ccaggaactt tccagcagta tctcgctgg tgaagacca gaggaagg 1380
gagtaaaact tggattggga gatttcattt tctacagtgt tctggttgg aaagcctcag 1440
caacagccag tggagactgg aacacaacca tagcctgttt cgtagccata ttaattggtt 1500
tgtgccttac attattactc cttgccattt tcaagaaagc attgccagct cttccaatct 1560
ccatcacctt tgggcttgtt ttctactttg ccacagatta tctgtacag ctttttatgg 1620
accaattagc attccatcaa ttttatatct agcatatttg cggttagaat cccatggatg 1680
tttcttcttt gactataaca aaatctgggg aggacaaagg tgattttcct gtgtccacat 1740
ctaacaaagt caagattccc ggctggactt ttgcagcttc cttccaagtc ttctgacca 1800
ccttgacta ttggactttg gaaggaggtg cctatagaaa acgattttga acatacttca 1860
tcgcagtga ctgtgtccct cgggtgcagaa actaccagat ttgagggacg aggtcaagga 1920
gatatgatag gcccggaagt tgctgtgccc catcagcagc ttgacgcgtg gtcacaggac 1980
gatttcactg acactgcaa ctctcaggac taccgttacc aagaggttag gtgaagtgg 2040
ttaaaccaaa cggaactctt catcttaaac tacacgttga aaatcaaccc aataattctg 2100
tattaactga attctgaact tttcaggagg tactgtgagg aagagcaggc accagcagca 2160
gaatggggaa tggagaggtg ggcaggggtt ccagcttccc tttgattttt tgctgcagac 2220
tcaccttttt taaatgagac ttgttttccc ctctctttga gtcaagtcaa atatgtagat 2280
tgcttttggc aattcttctt ctcaagcact gacactcatt accgtctgtg attgccattt 2340
cttccaagg ccagctgtaa cctgaggttg ctttatccta aaagttttaa cctcaggttc 2400
caaatcagc aaattttgga aacagtacag ctattttctca tcaattctct atcatgttga 2460
agtcaaatgt ggattttcca ccaaattctg aatttgtaga cataacttga cgtcacttg 2520
cccagatgc ctctctgtc ctcatcttc tctccacac aagcagctct tttctacagc 2580
cagtaaggca gctctgtcgt ggtagcagat ggtccatta ttctagggtc ttactctttg 2640
tatgatgaaa agaattgtgt atgaatcggt gctgtcagcc ctgctgtcag accttcttcc 2700
acagcaaatg agatgtatgc ccaaagcgtt agaattaaag aagagtaaaa tggtcttga 2760
agc 2763

```

&lt;210&gt; SEQ ID NO 8

&lt;211&gt; LENGTH: 467

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Homo Sapiens

&lt;400&gt; SEQUENCE: 8

```

Met Thr Glu Leu Pro Ala Pro Leu Ser Tyr Phe Gln Asn Ala Gln Met
1           5           10           15

```

```

Ser Glu Asp Asn His Leu Ser Asn Thr Val Arg Ser Gln Asn Asp Asn
20           25           30

```

```

Arg Glu Arg Gln Glu His Asn Asp Arg Arg Ser Leu Gly His Pro Glu
35           40           45

```

```

Pro Leu Ser Asn Gly Arg Pro Gln Gly Asn Ser Arg Gln Val Val Glu
50           55           60

```

```

Gln Asp Glu Glu Glu Asp Glu Glu Leu Thr Leu Lys Tyr Gly Ala Lys
65           70           75           80

```

```

His Val Ile Met Leu Phe Val Pro Val Thr Leu Cys Met Val Val Val
85           90           95

```

```

Val Ala Thr Ile Lys Ser Val Ser Phe Tyr Thr Arg Lys Asp Gly Gln

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| 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |     |     |     |  |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
| Leu | Ile | Tyr | Thr | Pro | Phe | Thr | Glu | Asp | Thr | Glu | Thr | Val | Gly | Gln | Arg |  |
| 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |     |     |  |
| Ala | Leu | His | Ser | Ile | Leu | Asn | Ala | Ala | Ile | Met | Ile | Ser | Val | Ile | Val |  |
| 130 |     |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |     |  |
| Val | Met | Thr | Ile | Leu | Leu | Val | Val | Leu | Tyr | Lys | Tyr | Arg | Cys | Tyr | Lys |  |
| 145 |     |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     | 160 |  |
| Val | Ile | His | Ala | Trp | Leu | Ile | Ile | Ser | Ser | Leu | Leu | Leu | Leu | Phe | Phe |  |
| 165 |     |     |     |     | 170 |     |     |     |     | 175 |     |     |     |     |     |  |
| Phe | Ser | Phe | Ile | Tyr | Leu | Gly | Glu | Val | Phe | Lys | Thr | Tyr | Asn | Val | Ala |  |
| 180 |     |     |     |     | 185 |     |     |     |     | 190 |     |     |     |     |     |  |
| Val | Asp | Tyr | Ile | Thr | Val | Ala | Leu | Leu | Ile | Trp | Asn | Phe | Gly | Val | Val |  |
| 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |     |     |  |
| Gly | Met | Ile | Ser | Ile | His | Trp | Lys | Gly | Pro | Leu | Arg | Leu | Gln | Gln | Ala |  |
| 210 |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |     |  |
| Tyr | Leu | Ile | Met | Ile | Ser | Ala | Leu | Met | Ala | Leu | Val | Phe | Ile | Lys | Tyr |  |
| 225 |     |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |  |
| Leu | Pro | Glu | Trp | Thr | Ala | Trp | Leu | Ile | Leu | Ala | Val | Ile | Ser | Val | Tyr |  |
| 245 |     |     |     |     | 250 |     |     |     |     | 255 |     |     |     |     |     |  |
| Asp | Leu | Val | Ala | Val | Leu | Cys | Pro | Lys | Gly | Pro | Leu | Arg | Met | Leu | Val |  |
| 260 |     |     |     |     | 265 |     |     |     |     | 270 |     |     |     |     |     |  |
| Glu | Thr | Ala | Gln | Glu | Arg | Asn | Glu | Thr | Leu | Phe | Pro | Ala | Leu | Ile | Tyr |  |
| 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |     |     |  |
| Ser | Ser | Thr | Met | Val | Trp | Leu | Val | Asn | Met | Ala | Glu | Gly | Asp | Pro | Glu |  |
| 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |     |  |
| Ala | Gln | Arg | Arg | Val | Ser | Lys | Asn | Ser | Lys | Tyr | Asn | Ala | Glu | Ser | Thr |  |
| 305 |     |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |  |
| Glu | Arg | Glu | Ser | Gln | Asp | Thr | Val | Ala | Glu | Asn | Asp | Asp | Gly | Gly | Phe |  |
| 325 |     |     |     |     | 330 |     |     |     |     | 335 |     |     |     |     |     |  |
| Ser | Glu | Glu | Trp | Glu | Ala | Gln | Arg | Asp | Ser | His | Leu | Gly | Pro | His | Arg |  |
| 340 |     |     |     |     | 345 |     |     |     |     | 350 |     |     |     |     |     |  |
| Ser | Thr | Pro | Glu | Ser | Arg | Ala | Ala | Val | Gln | Glu | Leu | Ser | Ser | Ser | Ile |  |
| 355 |     |     |     |     | 360 |     |     |     |     | 365 |     |     |     |     |     |  |
| Leu | Ala | Gly | Glu | Asp | Pro | Glu | Glu | Arg | Gly | Val | Lys | Leu | Gly | Leu | Gly |  |
| 370 |     |     |     |     | 375 |     |     |     |     | 380 |     |     |     |     |     |  |
| Asp | Phe | Ile | Phe | Tyr | Ser | Val | Leu | Val | Gly | Lys | Ala | Ser | Ala | Thr | Ala |  |
| 385 |     |     |     |     | 390 |     |     |     |     | 395 |     |     |     |     | 400 |  |
| Ser | Gly | Asp | Trp | Asn | Thr | Thr | Ile | Ala | Cys | Phe | Val | Ala | Ile | Leu | Ile |  |
| 405 |     |     |     |     | 410 |     |     |     |     | 415 |     |     |     |     |     |  |
| Gly | Leu | Cys | Leu | Thr | Leu | Leu | Leu | Leu | Ala | Ile | Phe | Lys | Lys | Ala | Leu |  |
| 420 |     |     |     |     | 425 |     |     |     |     | 430 |     |     |     |     |     |  |
| Pro | Ala | Leu | Pro | Ile | Ser | Ile | Thr | Phe | Gly | Leu | Val | Phe | Tyr | Phe | Ala |  |
| 435 |     |     |     |     | 440 |     |     |     |     | 445 |     |     |     |     |     |  |
| Thr | Asp | Tyr | Leu | Val | Gln | Pro | Phe | Met | Asp | Gln | Leu | Ala | Phe | His | Gln |  |
| 450 |     |     |     |     | 455 |     |     |     |     | 460 |     |     |     |     |     |  |
| Phe | Tyr | Ile |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
| 465 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |

<210> SEQ ID NO 9  
 <211> LENGTH: 1720  
 <212> TYPE: DNA  
 <213> ORGANISM: Porcine

<400> SEQUENCE: 9

aatcggaaac aaaacagcgg ctgctgggga agggacctgg gctgcgagag gtggcggctg

60

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cgacgagaaa gaacctaate cgggagcctg caacctgtga agttcttaga aagcttggcc 120
tgaggaggaa cacatgaaag aaagaacccc aggaggctct gatttctgtg aaaaagtatt 180
tctatacggg tgttccaatg acagagttac ctgcaccctt gtctacttcc cagaatgccc 240
agatgtccga ggacaaccac gtgagcaata acgtaagtag ccagaatgac agtagagagc 300
ggcatgagca cagcatcgag aggcggaggc gtggcaactc tgagtcgtta tccaatggcg 360
gagcccaggg aaactcacgc cagggtggtg aacaagaaga agaggaagac gaggagctga 420
cgttgaaata tggcgccaaa catgtgatca tgctctttgt cctgtgact ctatgtatgg 480
tgggtggtgt ggccaccatc aaatcagtc gcttttatac ccggaaggat gggcagctga 540
tctatactcc atttacagaa gacactgaga ctgtagggca gagagccctg cactcaattc 600
tgaatgctgc tatcatgatt agtgtcattg tcgtcatgac tattctcctg gtggttctct 660
ataaatacag gtgctataag gtcacccatg cctggcctat tatttcatcc ctattgttgc 720
tggtcttttt ctcatcatt tacttggggg aagtgtttaa aacctataac gttgccatgg 780
attacattac ggtggcactc ctgatctgga attttgggtg ggtaggaaatg attgccattc 840
actggaaagg cccattgcga ctccagcagg catatctcat tatgatcagt gccctcatgg 900
cctggtgttt tatcaagtac ctcccgaat ggacccgctg gctcatcttg gctgtgattt 960
cagtatacga ttttagtggt gttttgtgtc caaatggccc acttcgtttg ctggttgaaa 1020
cagctcagga gagaaatgaa actctctttc cagctcttat ttactcgtca acaatggtgt 1080
ggttggtgaa tatggcagaa ggagaccag aagcccaaag gaaggatatc aaaaactcca 1140
attataatgc acaaagcaca ggtgaatcac aagactctgt gacagagagt gatgatggtg 1200
gcttcagtga agagtgggaa gccagaggg acagtcgcct gggacctcat cactctacag 1260
ctgagtcacg atctgctgta caggatcttt ccagaagcat ccagaccact gaggaccag 1320
aagaaagggg agtaaaactt ggattaggag atttcatttt ctacagtgtt ctggttggtg 1380
aagctctctg aacagccagt ggagactgga acacaacat tgctgtttt gtagccatat 1440
taattgggtt gtgccttaca ttactgtctc tcgccatttt caagaaagcg ttgccagctc 1500
ttccaatctc tatcaccttt gggcttgttt tctactttgc cacagattat cttgtgcaac 1560
cctttatgga ccaattagca ttccatcaat tttatatcta gcataattcc agttagaatc 1620
tcatggattt tttctccttt ggctataata aaatctgggg aaagcaaagg tgattttgct 1680
gtgtccacat ctaacaaagt caggattccc agctggacct 1720

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<210> SEQ ID NO 10
<211> LENGTH: 467
<212> TYPE: PRT
<213> ORGANISM: Porcine

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<400> SEQUENCE: 10

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```

Met Thr Glu Leu Pro Ala Pro Leu Ser Tyr Phe Gln Asn Ala Gln Met
1           5           10           15
Ser Glu Asp Asn His Val Ser Asn Asn Val Ser Ser Gln Asn Asp Ser
20           25           30
Arg Glu Arg His Glu His Ser Ile Glu Arg Arg Arg Gly Asn Ser
35           40           45
Glu Ser Leu Ser Asn Gly Gly Ala Gln Gly Asn Ser Arg Gln Val Val
50           55           60
Glu Gln Glu Glu Glu Asp Glu Glu Leu Thr Leu Lys Tyr Gly Ala
65           70           75           80

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Lys His Val Ile Met Leu Phe Val Pro Val Thr Leu Cys Met Val Val  
                     85                                    90                                    95  
 Val Val Ala Thr Ile Lys Ser Val Ser Phe Tyr Thr Arg Lys Asp Gly  
                     100                                    105                                    110  
 Gln Leu Ile Tyr Thr Pro Phe Thr Glu Asp Thr Glu Thr Val Gly Gln  
                     115                                    120                                    125  
 Arg Ala Leu His Ser Ile Leu Asn Ala Ala Ile Met Ile Ser Val Ile  
                     130                                    135                                    140  
 Val Val Met Thr Ile Leu Leu Val Val Leu Tyr Lys Tyr Arg Cys Tyr  
                     145                                    150                                    155                                    160  
 Lys Val Ile His Ala Trp Leu Ile Ile Ser Ser Leu Leu Leu Leu Phe  
                     165                                    170                                    175  
 Phe Phe Ser Phe Ile Tyr Leu Gly Glu Val Phe Lys Thr Tyr Asn Val  
                     180                                    185                                    190  
 Ala Met Asp Tyr Ile Thr Val Ala Leu Leu Ile Trp Asn Phe Gly Val  
                     195                                    200                                    205  
 Val Gly Met Ile Ala Ile His Trp Lys Gly Pro Leu Arg Leu Gln Gln  
                     210                                    215                                    220  
 Ala Tyr Leu Ile Met Ile Ser Ala Leu Met Ala Leu Val Phe Ile Lys  
                     225                                    230                                    235                                    240  
 Tyr Leu Pro Glu Trp Thr Ala Trp Leu Ile Leu Ala Val Ile Ser Val  
                     245                                    250                                    255  
 Tyr Asp Leu Val Ala Val Leu Cys Pro Asn Gly Pro Leu Arg Leu Leu  
                     260                                    265                                    270  
 Val Glu Thr Ala Gln Glu Arg Asn Glu Thr Leu Phe Pro Ala Leu Ile  
                     275                                    280                                    285  
 Tyr Ser Ser Thr Met Val Trp Leu Val Asn Met Ala Glu Gly Asp Pro  
                     290                                    295                                    300  
 Glu Ala Gln Arg Lys Val Ser Lys Asn Ser Asn Tyr Asn Ala Gln Ser  
                     305                                    310                                    315                                    320  
 Thr Gly Glu Ser Gln Asp Ser Val Thr Glu Ser Asp Asp Gly Gly Phe  
                     325                                    330                                    335  
 Ser Glu Glu Trp Glu Ala Gln Arg Asp Ser Arg Leu Gly Pro His His  
                     340                                    345                                    350  
 Ser Thr Ala Glu Ser Arg Ser Ala Val Gln Asp Leu Ser Arg Ser Ile  
                     355                                    360                                    365  
 Pro Ala Thr Glu Asp Pro Glu Glu Arg Gly Val Lys Leu Gly Leu Gly  
                     370                                    375                                    380  
 Asp Phe Ile Phe Tyr Ser Val Leu Val Gly Lys Ala Ser Ala Thr Ala  
                     385                                    390                                    395                                    400  
 Ser Gly Asp Trp Asn Thr Thr Ile Ala Cys Phe Val Ala Ile Leu Ile  
                     405                                    410                                    415  
 Gly Leu Cys Leu Thr Leu Leu Leu Leu Ala Ile Phe Lys Lys Ala Leu  
                     420                                    425                                    430  
 Pro Ala Leu Pro Ile Ser Ile Thr Phe Gly Leu Val Phe Tyr Phe Ala  
                     435                                    440                                    445  
 Thr Asp Tyr Leu Val Gln Pro Phe Met Asp Gln Leu Ala Phe His Gln  
                     450                                    455                                    460  
 Phe Tyr Ile  
 465

<210> SEQ ID NO 11  
 <211> LENGTH: 467  
 <212> TYPE: PRT  
 <213> ORGANISM: Porcine

-continued

&lt;400&gt; SEQUENCE: 11

Met Thr Glu Leu Pro Ala Pro Leu Ser Tyr Phe Gln Asn Ala Gln Met  
 1 5 10 15  
 Ser Glu Asp Asn His Val Ser Asn Asn Val Ser Ser Gln Asn Asp Ser  
 20 25 30  
 Arg Glu Arg His Glu His Ser Ile Glu Arg Arg Arg Arg Gly Asn Ser  
 35 40 45  
 Glu Ser Leu Ser Asn Gly Gly Ala Gln Gly Asn Ser Arg Gln Val Val  
 50 55 60  
 Glu Gln Glu Glu Glu Glu Asp Glu Glu Leu Thr Leu Lys Tyr Gly Ala  
 65 70 75 80  
 Lys His Val Ile Met Leu Phe Val Pro Val Thr Leu Cys Met Val Val  
 85 90 95  
 Val Val Ala Thr Ile Lys Ser Val Ser Phe Tyr Thr Arg Lys Asp Gly  
 100 105 110  
 Gln Leu Ile Tyr Thr Pro Phe Thr Glu Asp Thr Glu Thr Val Gly Gln  
 115 120 125  
 Arg Ala Leu His Ser Ile Leu Asn Ala Ala Ile Met Thr Ser Val Ile  
 130 135 140  
 Val Val Met Thr Ile Leu Leu Val Val Leu Tyr Lys Tyr Arg Cys Tyr  
 145 150 155 160  
 Lys Val Ile His Ala Trp Leu Ile Ile Ser Ser Leu Leu Leu Leu Phe  
 165 170 175  
 Phe Phe Ser Phe Ile Tyr Leu Gly Glu Val Phe Lys Thr Tyr Asn Val  
 180 185 190  
 Ala Met Asp Tyr Ile Thr Val Ala Leu Leu Ile Trp Asn Phe Gly Val  
 195 200 205  
 Val Gly Met Ile Ala Ile His Trp Lys Gly Pro Leu Arg Leu Gln Gln  
 210 215 220  
 Ala Tyr Leu Ile Met Ile Ser Ala Leu Met Ala Leu Val Phe Ile Lys  
 225 230 235 240  
 Tyr Leu Pro Glu Trp Thr Ala Trp Leu Ile Leu Ala Val Ile Ser Val  
 245 250 255  
 Tyr Asp Leu Val Ala Val Leu Cys Pro Asn Gly Pro Leu Arg Leu Leu  
 260 265 270  
 Val Glu Thr Ala Gln Glu Arg Asn Glu Thr Leu Phe Pro Ala Leu Ile  
 275 280 285  
 Tyr Ser Ser Thr Met Val Trp Leu Val Asn Met Ala Glu Gly Asp Pro  
 290 295 300  
 Glu Ala Gln Arg Lys Val Ser Lys Asn Ser Asn Tyr Asn Ala Gln Ser  
 305 310 315 320  
 Thr Gly Glu Ser Gln Asp Ser Val Thr Glu Ser Asp Asp Gly Gly Phe  
 325 330 335  
 Ser Glu Glu Trp Glu Ala Gln Arg Asp Ser Arg Leu Gly Pro His His  
 340 345 350  
 Ser Thr Ala Glu Ser Arg Ser Ala Val Gln Asp Leu Ser Arg Ser Ile  
 355 360 365  
 Pro Ala Thr Glu Asp Pro Glu Glu Arg Gly Val Lys Leu Gly Leu Gly  
 370 375 380  
 Asp Phe Ile Phe Tyr Ser Val Leu Val Gly Lys Ala Ser Ala Thr Ala  
 385 390 395 400  
 Ser Gly Asp Trp Asn Thr Thr Ile Ala Cys Phe Val Ala Ile Leu Ile  
 405 410 415

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Gly Leu Cys Leu Thr Leu Leu Leu Leu Ala Ile Phe Lys Lys Ala Leu  
420 425 430

Pro Ala Leu Pro Ile Ser Ile Thr Phe Gly Leu Val Phe Tyr Phe Ala  
435 440 445

Thr Asp Tyr Leu Val Gln Pro Phe Met Asp Gln Leu Ala Phe His Gln  
450 455 460

Phe Tyr Ile  
465

<210> SEQ ID NO 12

<211> LENGTH: 2236

<212> TYPE: DNA

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 12

```

cgagcggcgg cggagcaggc atttcagca gtgaggagac agccagaagc aagctattgg      60
agctgaagga acctgagaca gaagctagtc cccctctga attttactga tgaagaaact      120
gaggccacag agctaaagt acttttccca aggtcgccca gcgaggacgt gggacttctc      180
agacgtcagg agagtgatgt gagggagctg tgtgaccata gaaagtgcg tgtaaaaaac      240
cagcgctgcc ctctttgaaa gccagggagc atcattcatt tagcctgctg agaagaagaa      300
accaagtgtc cgggattcag acctctctgc ggcccaagt gttcgtggcg cttccagagg      360
cagggctatg ctcacattca tggcctctga cagcgaggaa gaagtgtgtg atgagcggac      420
gtccctaatt tcggccgaga gcccacgcc gcgctcctgc caggagggca ggcaggggcc      480
agaggatgga gagaacactg cccagtggag aagccaggag aacgaggagg acggtgagga      540
ggacctgac cgctatgtct gtagtggggt tcccggcgg ccgccaggcc tggaggaaga      600
gctgaccctc aaatacggag cgaagcacgt gatcatgctg tttgtgcctg tcaactctgt      660
catgatcgtg gtggtagcca ccatcaagtc tgtgcgcttc tacacagaga agaatggaca      720
gctcatctac acgacattca ctgaggacac accctcggtg ggccagcgcc tctcaactc      780
cgtgctgaac accctcatca tgatcagcgt catcgtggtt atgaccatct tcttggtggt      840
gctctacaag taaccgtgct acaagtcat ccatggctgg ttgatcatgt cttactgat      900
gctgctgttc ctcttcacct atatctacct tggggaagtg ctcaagacct acaatgtggc      960
catggactac cccacctct tctgactgt ctggaacttc ggggcagtgg gcatggtgtg      1020
catccactgg aagggccctc tgggtgtgca gcaggcctac ctcacatga tcagtgcgct      1080
catggcccta gtgttcacat agtacctccc agagtgggtc gcgtgggtca tctgggcgc      1140
catctctgtg tatgatctcg tggctgtgct gtgtcccaa gggcctctga gaatgctggt      1200
agaaactgcc caggagagaa atgagcccat attcctgcc ctgatatact catctgccat      1260
gggtgtggac gtgtgcatgg cgaagctgga cccctcctct cagggtgccc tccagctccc      1320
ctacgacctg gagatggaag aagactccta tgacagtttt ggggagcctt cataccccga      1380
agtcttttag cctcccttga ctggctaccc aggggaggag ctggaggaag aggaggaaag      1440
gggcgtgaag cttggcctcg gggacttcat cttctacagt gtgctggtgg gcaaggcggc      1500
tgccacgggc agcggggact ggaataccac gctggcctgc ttcgtggcca tctcattgg      1560
cttgtgtctg accctcctgc tgcttctgtg gttcaagaag gcgctgccc cctccccat      1620
ctccatcacg ttcgggtcga tcttttactt ctccacggac aacctggtgc ggcggttcat      1680
ggacacctcg gcctcccatc agctctacat ctgagggaca tgggtgtgcca caggctgcaa      1740
gtgcaggga attttcattg gatgcagttg tatagtttta cactctagtg ccatatattt      1800

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ttaagacttt tctttcctta aaaaataaag tacgtgttta cttggtgagg aggaggcaga 1860
accagctcct tgggtgccagc tgtttcatca ccagactttg gctcccgtt tggggagcgc 1920
ctcgcttcac ggacaggaag cacagcaggt ttatccagat gaactgagaa ggtcagatta 1980
ggggggggag aagagcatcc ggcagtaggg ctgagatgcg caaagagtgt gctcgggagt 2040
ggccccctggc acctgggtgc tctggctgga gaggaaaagc cagttcccta cgaggagtgt 2100
tcccaatgct ttgtccatga tgctcttggt attttattgc ctttagaaac tgagtccgtg 2160
tcttggttacg gcagtcacac tgctgggaag tggcttaata gtaatatcaa taaatagatg 2220
agtcctgtta gaaaaa 2236

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&lt;210&gt; SEQ ID NO 13

&lt;211&gt; LENGTH: 448

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Homo Sapiens

&lt;400&gt; SEQUENCE: 13

```

Met Leu Thr Phe Met Ala Ser Asp Ser Glu Glu Glu Val Cys Asp Glu
1          5          10          15
Arg Thr Ser Leu Met Ser Ala Glu Ser Pro Thr Pro Arg Ser Cys Gln
20         25         30
Glu Gly Arg Gln Gly Pro Glu Asp Gly Glu Asn Thr Ala Gln Trp Arg
35         40         45
Ser Gln Glu Asn Glu Glu Asp Gly Glu Glu Asp Pro Asp Arg Tyr Val
50         55         60
Cys Ser Gly Val Pro Gly Arg Pro Pro Gly Leu Glu Glu Glu Leu Thr
65         70         75         80
Leu Lys Tyr Gly Ala Lys His Val Ile Met Leu Phe Val Pro Val Thr
85         90         95
Leu Cys Met Ile Val Val Val Ala Thr Ile Lys Ser Val Arg Phe Tyr
100        105        110
Thr Glu Lys Asn Gly Gln Leu Ile Tyr Thr Thr Phe Thr Glu Asp Thr
115        120        125
Pro Ser Val Gly Gln Arg Leu Leu Asn Ser Val Leu Asn Thr Leu Ile
130        135        140
Met Ile Ser Val Ile Val Val Met Thr Ile Phe Leu Val Val Leu Tyr
145        150        155        160
Lys Tyr Arg Cys Tyr Lys Phe Ile His Gly Trp Leu Ile Met Ser Ser
165        170        175
Leu Met Leu Leu Phe Leu Phe Thr Tyr Ile Tyr Leu Gly Glu Val Leu
180        185        190
Lys Thr Tyr Asn Val Ala Met Asp Tyr Pro Thr Leu Leu Leu Thr Val
195        200        205
Trp Asn Phe Gly Ala Val Gly Met Val Cys Ile His Trp Lys Gly Pro
210        215        220
Leu Val Leu Gln Gln Ala Tyr Leu Ile Met Ile Ser Ala Leu Met Ala
225        230        235        240
Leu Val Phe Ile Lys Tyr Leu Pro Glu Trp Ser Ala Trp Val Ile Leu
245        250        255
Gly Ala Ile Ser Val Tyr Asp Leu Val Ala Val Leu Cys Pro Lys Gly
260        265        270
Pro Leu Arg Met Leu Val Glu Thr Ala Gln Glu Arg Asn Glu Pro Ile
275        280        285
Phe Pro Ala Leu Ile Tyr Ser Ser Ala Met Val Trp Thr Val Gly Met

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| 290                                                                 | 295 | 300  |     |
|---------------------------------------------------------------------|-----|------|-----|
| Ala Lys Leu Asp Pro Ser Ser Gln Gly Ala Leu Gln Leu Pro Tyr Asp     |     |      |     |
| 305                                                                 | 310 | 315  | 320 |
| Pro Glu Met Glu Glu Asp Ser Tyr Asp Ser Phe Gly Glu Pro Ser Tyr     |     |      |     |
|                                                                     | 325 | 330  | 335 |
| Pro Glu Val Phe Glu Glu Pro Pro Leu Thr Gly Tyr Pro Gly Glu Glu Leu |     |      |     |
|                                                                     | 340 | 345  | 350 |
| Glu Glu Glu Glu Glu Arg Gly Val Lys Leu Gly Leu Gly Asp Phe Ile     |     |      |     |
|                                                                     | 355 | 360  | 365 |
| Phe Tyr Ser Val Leu Val Gly Lys Ala Ala Ala Thr Gly Ser Gly Asp     |     |      |     |
|                                                                     | 370 | 375  | 380 |
| Trp Asn Thr Thr Leu Ala Cys Phe Val Ala Ile Leu Ile Gly Leu Cys     |     |      |     |
|                                                                     | 385 | 390  | 395 |
| Leu Thr Leu Leu Leu Leu Ala Val Phe Lys Lys Ala Leu Pro Ala Leu     |     |      |     |
|                                                                     | 405 | 410  | 415 |
| Pro Ile Ser Ile Thr Phe Gly Leu Ile Phe Tyr Phe Ser Thr Asp Asn     |     |      |     |
|                                                                     | 420 | 425  | 430 |
| Leu Val Arg Pro Phe Met Asp Thr Leu Ala Ser His Gln Leu Tyr Ile     |     |      |     |
|                                                                     | 435 | 440  | 445 |
| <210> SEQ ID NO 14                                                  |     |      |     |
| <211> LENGTH: 1347                                                  |     |      |     |
| <212> TYPE: DNA                                                     |     |      |     |
| <213> ORGANISM: Porcine                                             |     |      |     |
| <400> SEQUENCE: 14                                                  |     |      |     |
| atgtctcactt tcatggcctc tgacagcgag gaagaagtgt gtgacgagcg gacgtccctg  |     | 60   |     |
| atgtcggccg agagccccac gcctcgctcc tgccaggaag gcaggcaggg cctggaggat   |     | 120  |     |
| ggagagagtg ctgctcagtg gagaagccag gacagcgagg aggaccacga ggaagaccct   |     | 180  |     |
| gaccgctatg tctgcagtgg ggttcctggc cggccaccag gcctggagga ggagctgacc   |     | 240  |     |
| ctcaaatatg gggcaaaagca cgtgatcatg ctctttgtgc ctgtcacgct gtgtatgatc  |     | 300  |     |
| gtggtagtgg ccaccatcaa gtccgtgcgc ttctacacag agaagaatgg acagctcatc   |     | 360  |     |
| tacacgccgt tcaccgagga cagcgcctcc gtgggccagc gcctcctcaa ctccgtgctc   |     | 420  |     |
| aacacctca tcatgatcag cgtcattgtc gtcatgacca tcttcctggg cgtgctctac    |     | 480  |     |
| aagtaccgct gctacaagtt catccacggc tggctgatca catcctccct gatgctgctc   |     | 540  |     |
| ttctcttca cctacatcta cctcggggaa gtgctcaaga cctacaacgt ggccatggac    |     | 600  |     |
| tacccacccc tgttcttgac cgtctggaac ttcggggcgg tgggcatggg gtgcatccac   |     | 660  |     |
| tggaagggcc ccctggtgct gcagcaggcc tacctcatca tgatcagcgc gctcatggcc   |     | 720  |     |
| ttggtgttca tcaagtacct ccgagtggtg tccgcctggg tcatcctggg cgccatctct   |     | 780  |     |
| gtgtacgatc tcgtggctgt gctgtgcccc aaagggccgc tgagaatggt ggtagaaact   |     | 840  |     |
| gcccaggaga gaaacgagcc catatttcct gccctgatat actcatctgc catggtgtgg   |     | 900  |     |
| acggtaggca tggccaagct ggaccctcc tctcagggag cccttcagct ccctacgac     |     | 960  |     |
| ccagagatgg aagaggactc ctatgacagt tttggggagc cttcgtaccc tgaagtcttt   |     | 1020 |     |
| gaacccccgc tgcttggtca cccggggcag gagctggagg aagaggagga aaggggcgtg   |     | 1080 |     |
| aagctgggcc tcggagactt catcttctac agcgtgctgg tgggcaaggc agcggccacg   |     | 1140 |     |
| ggcagcgggg actggaacac cacgtgggcc tgcttcgtgg ccctcctcat cggtttgtgt   |     | 1200 |     |
| ctgaccctcc tgctgctcgc ggtgttcaag aaagcgctac ccgcccttcc catctccatc   |     | 1260 |     |
| acgttcggcc tcatcttcta ttctccacc gacaacctgg tacggccttt catggacacg    |     | 1320 |     |

-continued

ctggcctccc accagctcta catctga

1347

&lt;210&gt; SEQ ID NO 15

&lt;211&gt; LENGTH: 448

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Porcine

&lt;400&gt; SEQUENCE: 15

```

Met Leu Thr Phe Met Ala Ser Asp Ser Glu Glu Glu Val Cys Asp Glu
1      5      10      15
Arg Thr Ser Leu Met Ser Ala Glu Ser Pro Thr Pro Arg Ser Cys Gln
20     25     30
Glu Gly Arg Gln Gly Leu Glu Asp Gly Glu Ser Ala Ala Gln Trp Arg
35     40     45
Ser Gln Asp Ser Glu Glu Asp His Glu Glu Asp Pro Asp Arg Tyr Val
50     55     60
Cys Ser Gly Val Pro Gly Arg Pro Pro Gly Leu Glu Glu Glu Leu Thr
65     70     75     80
Leu Lys Tyr Gly Ala Lys His Val Ile Met Leu Phe Val Pro Val Thr
85     90     95
Leu Cys Met Ile Val Val Val Ala Thr Ile Lys Ser Val Arg Phe Tyr
100    105    110
Thr Glu Lys Asn Gly Gln Leu Ile Tyr Thr Pro Phe Thr Glu Asp Thr
115    120    125
Pro Ser Val Gly Gln Arg Leu Leu Asn Ser Val Leu Asn Thr Leu Ile
130    135    140
Met Ile Ser Val Ile Val Val Met Thr Ile Phe Leu Val Val Leu Tyr
145    150    155    160
Lys Tyr Arg Cys Tyr Lys Phe Ile His Gly Trp Leu Ile Thr Ser Ser
165    170    175
Leu Met Leu Leu Phe Leu Phe Thr Tyr Ile Tyr Leu Gly Glu Val Leu
180    185    190
Lys Thr Tyr Asn Val Ala Met Asp Tyr Pro Thr Leu Phe Leu Thr Val
195    200    205
Trp Asn Phe Gly Ala Val Gly Met Val Cys Ile His Trp Lys Gly Pro
210    215    220
Leu Val Leu Gln Gln Ala Tyr Leu Ile Met Ile Ser Ala Leu Met Ala
225    230    235    240
Leu Val Phe Ile Lys Tyr Leu Pro Glu Trp Ser Ala Trp Val Ile Leu
245    250    255
Gly Ala Ile Ser Val Tyr Asp Leu Val Ala Val Leu Cys Pro Lys Gly
260    265    270
Pro Leu Arg Met Leu Val Glu Thr Ala Gln Glu Arg Asn Glu Pro Ile
275    280    285
Phe Pro Ala Leu Ile Tyr Ser Ser Ala Met Val Trp Thr Val Gly Met
290    295    300
Ala Lys Leu Asp Pro Ser Ser Gln Gly Ala Leu Gln Leu Pro Tyr Asp
305    310    315    320
Pro Glu Met Glu Glu Asp Ser Tyr Asp Ser Phe Gly Glu Pro Ser Tyr
325    330    335
Pro Glu Val Phe Glu Pro Pro Leu Pro Gly Tyr Pro Gly Glu Glu Leu
340    345    350
Glu Glu Glu Glu Glu Arg Gly Val Lys Leu Gly Leu Gly Asp Phe Ile
355    360    365

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Phe Tyr Ser Val Leu Val Gly Lys Ala Ala Ala Thr Gly Ser Gly Asp
 370                      375                      380

Trp Asn Thr Thr Leu Ala Cys Phe Val Ala Ile Leu Ile Gly Leu Cys
385                      390                      395                      400

Leu Thr Leu Leu Leu Leu Ala Val Phe Lys Lys Ala Leu Pro Ala Leu
                      405                      410                      415

Pro Ile Ser Ile Thr Phe Gly Leu Ile Phe Tyr Phe Ser Thr Asp Asn
                      420                      425                      430

Leu Val Arg Pro Phe Met Asp Thr Leu Ala Ser His Gln Leu Tyr Ile
 435                      440                      445

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<210> SEQ ID NO 16
<211> LENGTH: 449
<212> TYPE: PRT
<213> ORGANISM: Porcine

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<400> SEQUENCE: 16

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```

Ile Met Leu Thr Phe Met Ala Ser Asp Ser Glu Glu Glu Val Cys Asp
 1                      5                      10                      15

Glu Arg Thr Ser Leu Met Ser Ala Glu Ser Pro Thr Pro Arg Ser Cys
                      20                      25                      30

Gln Glu Gly Arg Gln Gly Leu Glu Asp Gly Glu Ser Ala Ala Gln Trp
 35                      40                      45

Arg Ser Gln Asp Ser Glu Glu Asp His Glu Glu Asp Pro Asp Arg Tyr
 50                      55                      60

Val Cys Ser Gly Val Pro Gly Arg Pro Pro Gly Leu Glu Glu Glu Leu
 65                      70                      75                      80

Thr Leu Lys Tyr Gly Ala Lys His Val Ile Met Leu Phe Val Pro Val
 85                      90                      95

Thr Leu Cys Met Ile Val Val Val Ala Thr Ile Lys Ser Val Arg Phe
 100                     105                     110

Tyr Thr Glu Lys Asn Gly Gln Leu Ile Tyr Thr Pro Phe Thr Glu Asp
 115                     120                     125

Thr Pro Ser Val Gly Gln Arg Leu Leu Asn Ser Val Leu Asn Thr Leu
 130                     135                     140

Ile Met Ile Ser Val Ile Val Val Met Thr Ile Phe Leu Val Val Leu
 145                     150                     155                     160

Tyr Lys Tyr Arg Cys Tyr Lys Phe Ile His Gly Trp Leu Ile Thr Ser
 165                     170                     175

Ser Leu Met Leu Leu Phe Leu Phe Thr Tyr Ile Tyr Leu Gly Glu Val
 180                     185                     190

Leu Lys Thr Tyr Asn Val Ala Met Asp Tyr Pro Thr Leu Phe Leu Thr
 195                     200                     205

Val Trp Asn Phe Gly Ala Val Gly Met Val Cys Ile His Trp Lys Gly
 210                     215                     220

Pro Leu Val Leu Gln Gln Ala Tyr Leu Ile Met Ile Ser Ala Leu Met
 225                     230                     235                     240

Ala Leu Val Phe Ile Lys Tyr Leu Pro Glu Trp Ser Ala Trp Val Ile
 245                     250                     255

Leu Gly Ala Ile Ser Val Tyr Asp Leu Val Ala Val Leu Cys Pro Lys
 260                     265                     270

Gly Pro Leu Arg Met Leu Val Glu Thr Ala Gln Glu Arg Asn Glu Pro
 275                     280                     285

Ile Phe Pro Ala Leu Ile Tyr Ser Ser Ala Met Val Trp Thr Val Gly
 290                     295                     300

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Met Ala Lys Leu Asp Pro Ser Ser Gln Gly Ala Leu Gln Leu Pro Tyr  
305 310 315 320

Asp Pro Glu Met Glu Glu Asp Ser Tyr Asp Ser Phe Gly Glu Pro Ser  
325 330 335

Tyr Pro Glu Val Phe Glu Pro Pro Leu Pro Gly Tyr Pro Gly Glu Glu  
340 345 350

Leu Glu Glu Glu Glu Glu Arg Gly Val Lys Leu Gly Leu Gly Asp Phe  
355 360 365

Ile Phe Tyr Ser Val Leu Val Gly Lys Ala Ala Ala Thr Gly Ser Gly  
370 375 380

Asp Trp Asn Thr Thr Leu Ala Cys Phe Val Ala Ile Leu Ile Gly Leu  
385 390 395 400

Cys Leu Thr Leu Leu Leu Leu Ala Val Phe Lys Lys Ala Leu Pro Ala  
405 410 415

Leu Pro Ile Ser Ile Thr Phe Gly Leu Ile Phe Tyr Phe Ser Thr Asp  
420 425 430

Asn Leu Val Arg Pro Phe Met Asp Thr Leu Ala Ser His Gln Leu Tyr  
435 440 445

Ile

<210> SEQ ID NO 17

<211> LENGTH: 3641

<212> TYPE: DNA

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 17

```

gctgactcgc ctggctctga gccccgccgc cgcgctcggg ctccgtcagt ttcctcggca    60
gcggtaggcg agagcacgcg gaggagcgtg cgcggggggc ccgggagacg gcggcgggtg    120
cggcgccggc agagcaagga cgcggcggat cccactcgca cagcagcgca ctcggtgccc    180
cgcgcagggg cgcgatgctg cccggttttg cactgctcct gctggccgcc tggacggctc    240
gggcgctgga ggtaccact gatggtaatg ctggcctgct ggctgaaccc cagattgcca    300
tgttctgtgg cagactgaac atgcacatga atgtccagaa tgggaagtgg gattcagatc    360
catcagggac caaaactgc attgatacca aggaaggcat cctgcagtat tgccaagaag    420
tctacctga actgcagatc accaatgtgg tagaagccaa ccaaccagt accatccaga    480
actggtgcaa gcggggccgc aagcagtgca agacccatcc ccaactttgtg attccctacc    540
gctgcttagt tggtagtttt gtaagtgatg cccttctcgt tctgacaag tgcaaattct    600
tacaccagga gaggatggat gtttgcgaaa ctcacttcca ctggcacacc gtcgccaaag    660
agacatgcag tgagaagagt accaacttgc atgactacgg catgttgctg cctgcgggaa    720
ttgacaagtt ccgaggggta gagtttgtgt gttgccact ggctgaagaa agtgacaatg    780
tggattctgc tgatgcggag gaggatgact cggatgtctg gtggggcgga gcagacacag    840
actatgcaga tgggagtga gacaaagtag tagaagtagc agaggaggaa gaagtggctg    900
aggtggaaga agaagaagcc gatgatgacg aggacgatga ggatgggat gaggtagagg    960
aagaggtga ggaacctac gaagaagcca cagagagaac caccagcatt gccaccacca   1020
ccaccaccac cacagagtct gtggaagagg tggttcgaga ggtgtgctct gaacaagccg   1080
agacggggcc gtgccgagca atgatctccc gctggtactt tgatgtgact gaagggaagt   1140
gtgccccatt cttttacggc ggatgtggcg gcaaccggaa caactttgac acagaagagt   1200
actgcatggc cgtgtgtggc agcgccatgt cccaaagttt actcaagact acccaggaac   1260
ctcttgcccc agatcctgtt aaacttccta caacagcagc cagtaccctt gatgccgttg   1320

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|                                                                    |      |
|--------------------------------------------------------------------|------|
| acaagtatct cgagacacct ggggatgaga atgaacatgc ccatttccag aaagccaaag  | 1380 |
| agaggcttga ggccaagcac cgagagagaa tgtcccaggt catgagagaa tgggaagagg  | 1440 |
| cagaacgtca agcaaagaac ttgcctaaag ctgataagaa ggcagttatc cagcatttcc  | 1500 |
| aggagaaagt ggaatctttg gaacaggaag cagccaacga gagacagcag ctggtggaga  | 1560 |
| cacacatggc cagagtggaa gccatgctca atgaccgccg ccgcctggcc ctggagaact  | 1620 |
| acatcaccgc tctgcaggct gttcctcttc ggctctgca cgtgttcaat atgctaaga    | 1680 |
| agtatgtccg cgcagaacag aaggacagac agcacaccct aaagcatttc gagcatgtgc  | 1740 |
| gcatggtgga tcccaagaaa gccgctcaga tccggtccca ggttatgaca cacctccgtg  | 1800 |
| tgatttatga gcgcataaat cagtctctct ccttgcctca caacgtgcct gcagtggccg  | 1860 |
| aggagattca ggatgaagtt gatgagctgc ttcagaaaga gcaaaactat tcagatgacg  | 1920 |
| tcttgccaa catgattagt gaaccaagga tcagttacgg aaacgatgct ctcatgccat   | 1980 |
| ctttgaccga aacgaaaacc accgtggagc tccttcccggt gaatggagag ttcagcctgg | 2040 |
| acgatctcca gccgtggcat tcttttgggg ctgactctgt gccagccaac acagaaaacg  | 2100 |
| aagttgagcc tgttgatgcc cgccctgctg ccgaccgagg actgaccact cgaccagggt  | 2160 |
| ctgggttgac aaatatcaag acggaggaga tctctgaagt gaagatggat gcagaattcc  | 2220 |
| gacatgactc aggatatgaa gttcatcatc aaaaattggg gttctttgca gaagatgtgg  | 2280 |
| gttcaaaaca aggtgaatc attggactca tgggtggcgg tgtgtcata gcgacagtga    | 2340 |
| tcgtcatcac cttggtgatg ctgaagaaga aacagtacac atccattcat catggtgtgg  | 2400 |
| tggaggttga cgcgctgtgc accccagagg agcgcacact gtccaagatg cagcagaacg  | 2460 |
| gctacgaaaa tccaacctac aagttctttg agcagatgca gaactagacc cccgccacag  | 2520 |
| cagcctctga agttggacag caaaaaccatt gcttcactac ccacgggtgt ccatttatag | 2580 |
| aataatgtgg gaagaacaa acccgtttta tgatttactc attatcgctc tttgacagct   | 2640 |
| gtgctgtaac acaagtagat gcctgaactt gaattaatcc acacatcagt aatgtattct  | 2700 |
| atctctcttt acattttggt ctctatacta cattattaat gggttttgtg tactgtaaag  | 2760 |
| aatttagctg tatcaaacta gtgcatgaat agattctctc ctgattattt atcacatagc  | 2820 |
| cccttagcca gttgtatatt attcttggg tttgtgaccc aattaagtcc tactttacat   | 2880 |
| atgctttaag aatcgatggg ggatgcttca tgtgaacgtg ggagttcagc tgettctctt  | 2940 |
| gcctaagtat tcctttcctg atcactatgc attttaaagt taaacatttt taagtatttc  | 3000 |
| agatgcttta gagagatttt ttttccatga ctgcatttta ctgtacagat tgctgcttct  | 3060 |
| gctatatattg tgatatagga attaagagga tacacacggt tgtttctctg tgctgtttt  | 3120 |
| atgtgcacac attaggcatt gagacttcaa gcttttcttt tttgtccac gtatctttgg   | 3180 |
| gtctttgata aagaaaagaa tccctgttca ttgtaagcac ttttacgggg cgggtgggga  | 3240 |
| gggggtgctct gctggtcttc aattaccaag aattctccaa aacaattttc tgcaggatga | 3300 |
| ttgtacagaa tcattgctta tgacatgacg gctttctaca ctgtattaca taaataaatt  | 3360 |
| aaataaaata accccgggca agacttttct ttgaaggatg actacagaca ttaataaatc  | 3420 |
| gaagtaattt tgggtgggga gaagaggcag attcaatttt cttaaccag tctgaagttt   | 3480 |
| catttatgat acaaaagaag atgaaaatgg aagtggcaat ataaggggat gaggaaggca  | 3540 |
| tgcttggaac aaccctctct ttaagatgtg tcttcaattt gtataaaatg gtgttttcat  | 3600 |
| gtaaataaat acattcttgg aggagcaaaa aaaaaaaaaa a                      | 3641 |

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<210> SEQ ID NO 18
<211> LENGTH: 770
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 18
Met Leu Pro Gly Leu Ala Leu Leu Leu Leu Ala Ala Trp Thr Ala Arg
1          5          10          15
Ala Leu Glu Val Pro Thr Asp Gly Asn Ala Gly Leu Leu Ala Glu Pro
20          25          30
Gln Ile Ala Met Phe Cys Gly Arg Leu Asn Met His Met Asn Val Gln
35          40          45
Asn Gly Lys Trp Asp Ser Asp Pro Ser Gly Thr Lys Thr Cys Ile Asp
50          55          60
Thr Lys Glu Gly Ile Leu Gln Tyr Cys Gln Glu Val Tyr Pro Glu Leu
65          70          75          80
Gln Ile Thr Asn Val Val Glu Ala Asn Gln Pro Val Thr Ile Gln Asn
85          90          95
Trp Cys Lys Arg Gly Arg Lys Gln Cys Lys Thr His Pro His Phe Val
100         105         110
Ile Pro Tyr Arg Cys Leu Val Gly Glu Phe Val Ser Asp Ala Leu Leu
115         120         125
Val Pro Asp Lys Cys Lys Phe Leu His Gln Glu Arg Met Asp Val Cys
130         135         140
Glu Thr His Leu His Trp His Thr Val Ala Lys Glu Thr Cys Ser Glu
145         150         155         160
Lys Ser Thr Asn Leu His Asp Tyr Gly Met Leu Leu Pro Cys Gly Ile
165         170         175
Asp Lys Phe Arg Gly Val Glu Phe Val Cys Cys Pro Leu Ala Glu Glu
180         185         190
Ser Asp Asn Val Asp Ser Ala Asp Ala Glu Glu Asp Asp Ser Asp Val
195         200         205
Trp Trp Gly Gly Ala Asp Thr Asp Tyr Ala Asp Gly Ser Glu Asp Lys
210         215         220
Val Val Glu Val Ala Glu Glu Glu Glu Val Ala Glu Val Glu Glu Glu
225         230         235         240
Glu Ala Asp Asp Asp Glu Asp Asp Glu Asp Gly Asp Glu Val Glu Glu
245         250         255
Glu Ala Glu Glu Pro Tyr Glu Glu Ala Thr Glu Arg Thr Thr Ser Ile
260         265         270
Ala Thr Thr Thr Thr Thr Thr Thr Glu Ser Val Glu Glu Val Val Arg
275         280         285
Glu Val Cys Ser Glu Gln Ala Glu Thr Gly Pro Cys Arg Ala Met Ile
290         295         300
Ser Arg Trp Tyr Phe Asp Val Thr Glu Gly Lys Cys Ala Pro Phe Phe
305         310         315         320
Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp Thr Glu Glu Tyr
325         330         335
Cys Met Ala Val Cys Gly Ser Ala Met Ser Gln Ser Leu Leu Lys Thr
340         345         350
Thr Gln Glu Pro Leu Ala Arg Asp Pro Val Lys Leu Pro Thr Thr Ala
355         360         365
Ala Ser Thr Pro Asp Ala Val Asp Lys Tyr Leu Glu Thr Pro Gly Asp
370         375         380
Glu Asn Glu His Ala His Phe Gln Lys Ala Lys Glu Arg Leu Glu Ala

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|                                                                 |     |     |     |
|-----------------------------------------------------------------|-----|-----|-----|
| 385                                                             | 390 | 395 | 400 |
| Lys His Arg Glu Arg Met Ser Gln Val Met Arg Glu Trp Glu Glu Ala | 405 | 410 | 415 |
| Glu Arg Gln Ala Lys Asn Leu Pro Lys Ala Asp Lys Lys Ala Val Ile | 420 | 425 | 430 |
| Gln His Phe Gln Glu Lys Val Glu Ser Leu Glu Gln Glu Ala Ala Asn | 435 | 440 | 445 |
| Glu Arg Gln Gln Leu Val Glu Thr His Met Ala Arg Val Glu Ala Met | 450 | 455 | 460 |
| Leu Asn Asp Arg Arg Arg Leu Ala Leu Glu Asn Tyr Ile Thr Ala Leu | 465 | 470 | 475 |
| Gln Ala Val Pro Pro Arg Pro Arg His Val Phe Asn Met Leu Lys Lys | 485 | 490 | 495 |
| Tyr Val Arg Ala Glu Gln Lys Asp Arg Gln His Thr Leu Lys His Phe | 500 | 505 | 510 |
| Glu His Val Arg Met Val Asp Pro Lys Lys Ala Ala Gln Ile Arg Ser | 515 | 520 | 525 |
| Gln Val Met Thr His Leu Arg Val Ile Tyr Glu Arg Met Asn Gln Ser | 530 | 535 | 540 |
| Leu Ser Leu Leu Tyr Asn Val Pro Ala Val Ala Glu Glu Ile Gln Asp | 545 | 550 | 555 |
| Glu Val Asp Glu Leu Leu Gln Lys Glu Gln Asn Tyr Ser Asp Asp Val | 565 | 570 | 575 |
| Leu Ala Asn Met Ile Ser Glu Pro Arg Ile Ser Tyr Gly Asn Asp Ala | 580 | 585 | 590 |
| Leu Met Pro Ser Leu Thr Glu Thr Lys Thr Thr Val Glu Leu Leu Pro | 595 | 600 | 605 |
| Val Asn Gly Glu Phe Ser Leu Asp Asp Leu Gln Pro Trp His Ser Phe | 610 | 615 | 620 |
| Gly Ala Asp Ser Val Pro Ala Asn Thr Glu Asn Glu Val Glu Pro Val | 625 | 630 | 635 |
| Asp Ala Arg Pro Ala Ala Asp Arg Gly Leu Thr Thr Arg Pro Gly Ser | 645 | 650 | 655 |
| Gly Leu Thr Asn Ile Lys Thr Glu Glu Ile Ser Glu Val Lys Met Asp | 660 | 665 | 670 |
| Ala Glu Phe Arg His Asp Ser Gly Tyr Glu Val His His Gln Lys Leu | 675 | 680 | 685 |
| Val Phe Phe Ala Glu Asp Val Gly Ser Asn Lys Gly Ala Ile Ile Gly | 690 | 695 | 700 |
| Leu Met Val Gly Gly Val Val Ile Ala Thr Val Ile Val Ile Thr Leu | 705 | 710 | 715 |
| Val Met Leu Lys Lys Lys Gln Tyr Thr Ser Ile His His Gly Val Val | 725 | 730 | 735 |
| Glu Val Asp Ala Ala Val Thr Pro Glu Glu Arg His Leu Ser Lys Met | 740 | 745 | 750 |
| Gln Gln Asn Gly Tyr Glu Asn Pro Thr Tyr Lys Phe Phe Glu Gln Met | 755 | 760 | 765 |
| Gln Asn                                                         | 770 |     |     |

<210> SEQ ID NO 19  
 <211> LENGTH: 2088  
 <212> TYPE: DNA  
 <213> ORGANISM: Porcine

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&lt;400&gt; SEQUENCE: 19

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atgctgcccc gtttgccact ggtcctgctg gccgectgga cggtcggggc gctggaggtg    60
cccactgatg gcaatgccgg cctgcttgca gaaccccagg ttgccatgtt ctgtggcaaa    120
ctcaacatgc acatgaatgt gcagaatggg aagtgggagt cagatccgtc ggggaccaa    180
acctgcattg gcaccaagga aggcactctg cagtactgcc aagaagtcta cctgaactg    240
cagatcacca atgtggtaga agccaacaa ccagtgacca tccagaactg gtgcaagagg    300
agccggaagc agtgcaagac ccacactcac attgtgattc cgtaccgtg cttagttggc    360
gagtttgtaa gcgatgccct ccttgctccg gacaagtga agttcttaca ccaggagagg    420
atggatgttt gcgaaaccca ccttactcgg cactactgtg ccaagagac ctgtagttag    480
aagagtacga acttgcatga ctatggcatg ttgctgccct gtggaattga caagttccga    540
ggggtggagt ttgtgtgttg cccactggcc gaggaaagtg acaatatcga ctacagcagat    600
gcagaagagg atgactcgga cgtctggtgg ggtggagcag atacagacta tgcagatggc    660
agtgaagaca aagtcgtgga ggtcgcagag gaggaggaag tggctgatgt cgaggaagaa    720
gaagctgagg atgatgagga tgatgaggat ggtgatgagg tagaagaaga ggctgaggaa    780
ccctatgaag aggccacgga gagaaccacc agcatcgcca caaccaccac caccaccacg    840
gagtcctgtg aagaggtagt ccgagttcct acaacagcag ccagcacccc ggatgccgtt    900
gacaagtatc ttgagacacc tggagatgag aacgaacatg cgcatttcca gaaagccaaa    960
gagaggctgg aggccaagca ccgcgagaga atgtcccagg tcatgagaga gtgggaagag   1020
gcagaacgtc aagcaaaaga cttgcctaaa gctgataaga aagcagtgat ccagcatttc   1080
caggagaaaag tggagtctct ggagcaggaa gcagccaacg agaggcagca gttggtggag   1140
acgcacatgg ccagagtgga ggccatgctt aacgaccgcc ggccgctggc cctggagaat   1200
tacatcacgg ctcttcaggc tgttcctcct cggcctcgtc atgtgttcaa catgctcaag   1260
aagtatgtcc gtgctgaaca gaaagacaga cagcacaccc taaagcattt tgaacacgtt   1320
cgcatggtag atccaagaa agctgctcag atccgatccc aggttatgac acacctccgt   1380
gtgatattac agcgcataaa ccagtctctc tccctgctct acaacgttcc tgcgtgggcc   1440
gaggaaaattc aggatgaagt tgatgagctg ctgcagaaag agcaaaaacta ctcgatgat   1500
gtcttgacca acatgatcag cgaaccgagg atcagttatg gaaacgatgc tctcatgccg   1560
tctctgactg aaacaaaaac caccgtggag cttcttctct tgaatggaga gttcagcctg   1620
gatgatctcc agccctggca tcccttttgg gtagactctg tgcttgccaa cacagaaaat   1680
gaagtcgagc ctgttgacgc ccgccctgca gccgaccgag gactgaccac tcgaccaggt   1740
tccgggttga ccaacatcaa gacggaagag atctctgaag tgaagatgga tgcggagttc   1800
cgacacgatt cgggctatga ggttcacac caaaaactgg tgttcttcgc agaagatgtg   1860
ggttcaaaca aaggtgccat cattggactc atggtgggtg gtgttgtcat agcaaccgtg   1920
attgtcatca cttagttagt gctgaagaag aaacagtaca catctatcca tcacggtgtg   1980
gtggagggtg acgcagctgt gaccccgagg gagcgccacc tctccaagat gcagcagaat   2040
ggctatgaaa acccaactta caagttcttt gagcagatgc agaactag                2088

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&lt;210&gt; SEQ ID NO 20

&lt;211&gt; LENGTH: 695

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Porcine

&lt;400&gt; SEQUENCE: 20

|            |            |            |            |          |            |            |            |            |            |            |            |            |            |            |            |
|------------|------------|------------|------------|----------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| Met<br>1   | Leu        | Pro        | Gly        | Leu<br>5 | Ala        | Leu        | Val        | Leu        | Leu<br>10  | Ala        | Ala        | Trp        | Thr        | Ala<br>15  | Arg        |
| Ala        | Leu        | Glu        | Val<br>20  | Pro      | Thr        | Asp        | Gly        | Asn<br>25  | Ala        | Gly        | Leu        | Leu        | Ala<br>30  | Glu        | Pro        |
| Gln        | Val        | Ala<br>35  | Met        | Phe      | Cys        | Gly        | Lys<br>40  | Leu        | Asn        | Met        | His        | Met<br>45  | Asn        | Val        | Gln        |
| Asn        | Gly<br>50  | Lys        | Trp        | Glu      | Ser        | Asp<br>55  | Pro        | Ser        | Gly        | Thr        | Lys<br>60  | Thr        | Cys        | Ile        | Gly        |
| Thr<br>65  | Lys        | Glu        | Gly        | Ile      | Leu<br>70  | Gln        | Tyr        | Cys        | Gln        | Glu<br>75  | Val        | Tyr        | Pro        | Glu        | Leu<br>80  |
| Gln        | Ile        | Thr        | Asn<br>85  | Val      | Val        | Glu        | Ala        | Asn<br>90  | Gln        | Pro        | Val        | Thr        | Ile        | Gln<br>95  | Asn        |
| Trp        | Cys        | Lys        | Arg<br>100 | Ser      | Arg        | Lys        | Gln        | Cys<br>105 | Lys        | Thr        | His        | Thr        | His<br>110 | Ile        | Val        |
| Ile        | Pro        | Tyr<br>115 | Arg        | Cys      | Leu        | Val        | Gly<br>120 | Glu        | Phe        | Val        | Ser        | Asp<br>125 | Ala        | Leu        | Leu        |
| Val        | Pro<br>130 | Asp        | Lys        | Cys      | Lys        | Phe<br>135 | Leu        | His        | Gln        | Glu        | Arg<br>140 | Met        | Asp        | Val        | Cys        |
| Glu<br>145 | Thr        | His        | Leu        | His      | Trp<br>150 | His        | Thr        | Val        | Ala        | Lys<br>155 | Glu        | Thr        | Cys        | Ser        | Glu<br>160 |
| Lys        | Ser        | Thr        | Asn<br>165 | Leu      | His        | Asp        | Tyr        | Gly        | Met<br>170 | Leu        | Leu        | Pro        | Cys        | Gly<br>175 | Ile        |
| Asp        | Lys        | Phe<br>180 | Arg        | Gly      | Val        | Glu        | Phe        | Val<br>185 | Cys        | Cys        | Pro        | Leu        | Ala<br>190 | Glu        | Glu        |
| Ser        | Asp        | Asn<br>195 | Ile        | Asp      | Ser        | Ala        | Asp<br>200 | Ala        | Glu        | Glu        | Asp        | Asp<br>205 | Ser        | Asp        | Val        |
| Trp        | Trp<br>210 | Gly        | Gly        | Ala      | Asp<br>215 | Thr        | Asp        | Tyr        | Ala        | Asp<br>220 | Gly        | Ser        | Glu        | Asp        | Lys        |
| Val<br>225 | Val        | Glu        | Val        | Ala      | Glu<br>230 | Glu        | Glu        | Glu        | Val        | Ala<br>235 | Asp        | Val        | Glu        | Glu        | Glu<br>240 |
| Glu        | Ala        | Glu        | Asp<br>245 | Asp      | Glu        | Asp        | Asp        | Glu        | Asp<br>250 | Gly        | Asp        | Glu        | Val        | Glu<br>255 | Glu        |
| Glu        | Ala        | Glu        | Glu<br>260 | Pro      | Tyr        | Glu        | Glu        | Ala<br>265 | Thr        | Glu        | Arg        | Thr        | Thr<br>270 | Ser        | Ile        |
| Ala        | Thr        | Thr<br>275 | Thr        | Thr      | Thr        | Thr        | Thr        | Glu<br>280 | Ser        | Val        | Glu        | Glu        | Val<br>285 | Val        | Arg        |
| Val        | Pro<br>290 | Thr        | Thr        | Ala      | Ala        | Ser<br>295 | Thr        | Pro        | Asp        | Ala<br>300 | Val        | Asp        | Lys        | Tyr        | Leu        |
| Glu<br>305 | Thr        | Pro        | Gly        | Asp      | Glu<br>310 | Asn        | Glu        | His        | Ala        | His<br>315 | Phe        | Gln        | Lys        | Ala        | Lys<br>320 |
| Glu        | Arg        | Leu        | Glu<br>325 | Ala      | Lys        | His        | Arg        | Glu        | Arg<br>330 | Met        | Ser        | Gln        | Val        | Met<br>335 | Arg        |
| Glu        | Trp        | Glu<br>340 | Glu        | Ala      | Glu        | Arg        | Gln        | Ala<br>345 | Lys        | Asn        | Leu        | Pro        | Lys<br>350 | Ala        | Asp        |
| Lys        | Lys<br>355 | Ala        | Val        | Ile      | Gln        | His        | Phe<br>360 | Gln        | Glu        | Lys        | Val        | Glu<br>365 | Ser        | Leu        | Glu        |
| Gln<br>370 | Glu        | Ala        | Ala        | Asn      | Glu<br>375 | Arg        | Gln        | Gln        | Leu        | Val<br>380 | Glu        | Thr        | His        | Met        | Ala        |
| Arg<br>385 | Val        | Glu        | Ala        | Met      | Leu<br>390 | Asn        | Asp        | Arg        | Arg        | Arg<br>395 | Leu        | Ala        | Leu        | Glu        | Asn<br>400 |
| Tyr        | Ile        | Thr        | Ala<br>405 | Leu      | Gln        | Ala        | Val        | Pro        | Pro<br>410 | Arg        | Pro        | Arg        | His        | Val<br>415 | Phe        |
| Asn        | Met        | Leu<br>420 | Lys        | Lys      | Tyr        | Val        | Arg        | Ala<br>425 | Glu        | Gln        | Lys        | Asp<br>430 | Arg        | Gln        | His        |

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Thr Leu Lys His Phe Glu His Val Arg Met Val Asp Pro Lys Lys Ala  
 435 440 445  
 Ala Gln Ile Arg Ser Gln Val Met Thr His Leu Arg Val Ile Tyr Glu  
 450 455 460  
 Arg Met Asn Gln Ser Leu Ser Leu Leu Tyr Asn Val Pro Ala Val Ala  
 465 470 475 480  
 Glu Glu Ile Gln Asp Glu Val Asp Glu Leu Leu Gln Lys Glu Gln Asn  
 485 490 495  
 Tyr Ser Asp Asp Val Leu Ala Asn Met Ile Ser Glu Pro Arg Ile Ser  
 500 505 510  
 Tyr Gly Asn Asp Ala Leu Met Pro Ser Leu Thr Glu Thr Lys Thr Thr  
 515 520 525  
 Val Glu Leu Leu Pro Val Asn Gly Glu Phe Ser Leu Asp Asp Leu Gln  
 530 535 540  
 Pro Trp His Pro Phe Gly Val Asp Ser Val Pro Ala Asn Thr Glu Asn  
 545 550 555 560  
 Glu Val Glu Pro Val Asp Ala Arg Pro Ala Ala Asp Arg Gly Leu Thr  
 565 570 575  
 Thr Arg Pro Gly Ser Gly Leu Thr Asn Ile Lys Thr Glu Glu Ile Ser  
 580 585 590  
 Glu Val Lys Met Asp Ala Glu Phe Arg His Asp Ser Gly Tyr Glu Val  
 595 600 605  
 His His Gln Lys Leu Val Phe Phe Ala Glu Asp Val Gly Ser Asn Lys  
 610 615 620  
 Gly Ala Ile Ile Gly Leu Met Val Gly Gly Val Val Ile Ala Thr Val  
 625 630 635 640  
 Ile Val Ile Thr Leu Val Met Leu Lys Lys Lys Gln Tyr Thr Ser Ile  
 645 650 655  
 His His Gly Val Val Glu Val Asp Ala Ala Val Thr Pro Glu Glu Arg  
 660 665 670  
 His Leu Ser Lys Met Gln Gln Asn Gly Tyr Glu Asn Pro Thr Tyr Lys  
 675 680 685  
 Phe Phe Glu Gln Met Gln Asn  
 690 695

<210> SEQ ID NO 21  
 <211> LENGTH: 695  
 <212> TYPE: PRT  
 <213> ORGANISM: Porcine

<400> SEQUENCE: 21

Met Leu Pro Gly Leu Ala Leu Val Leu Leu Ala Ala Trp Thr Ala Arg  
 1 5 10 15  
 Ala Leu Glu Val Pro Thr Asp Gly Asn Ala Gly Leu Leu Ala Glu Pro  
 20 25 30  
 Gln Val Ala Met Phe Cys Gly Lys Leu Asn Met His Met Asn Val Gln  
 35 40 45  
 Asn Gly Lys Trp Glu Ser Asp Pro Ser Gly Thr Lys Thr Cys Ile Gly  
 50 55 60  
 Thr Lys Glu Gly Ile Leu Gln Tyr Cys Gln Glu Val Tyr Pro Glu Leu  
 65 70 75 80  
 Gln Ile Thr Asn Val Val Glu Ala Asn Gln Pro Val Thr Ile Gln Asn  
 85 90 95  
 Trp Cys Lys Arg Ser Arg Lys Gln Cys Lys Thr His Thr His Ile Val  
 100 105 110

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Ile Pro Tyr Arg Cys Leu Val Gly Glu Phe Val Ser Asp Ala Leu Leu  
 115 120 125  
 Val Pro Asp Lys Cys Lys Phe Leu His Gln Glu Arg Met Asp Val Cys  
 130 135 140  
 Glu Thr His Leu His Trp His Thr Val Ala Lys Glu Thr Cys Ser Glu  
 145 150 155 160  
 Lys Ser Thr Asn Leu His Asp Tyr Gly Met Leu Leu Pro Cys Gly Ile  
 165 170 175  
 Asp Lys Phe Arg Gly Val Glu Phe Val Cys Cys Pro Leu Ala Glu Glu  
 180 185 190  
 Ser Asp Asn Ile Asp Ser Ala Asp Ala Glu Glu Asp Asp Ser Asp Val  
 195 200 205  
 Trp Trp Gly Gly Ala Asp Thr Asp Tyr Ala Asp Gly Ser Glu Asp Lys  
 210 215 220  
 Val Val Glu Val Ala Glu Glu Glu Glu Val Ala Asp Val Glu Glu Glu  
 225 230 235 240  
 Glu Ala Glu Asp Asp Glu Asp Asp Glu Asp Gly Asp Glu Val Glu Glu  
 245 250 255  
 Glu Ala Glu Glu Pro Tyr Glu Glu Ala Thr Glu Arg Thr Thr Ser Ile  
 260 265 270  
 Ala Thr Thr Thr Thr Thr Thr Thr Glu Ser Val Glu Glu Val Val Arg  
 275 280 285  
 Val Pro Thr Thr Ala Ala Ser Thr Pro Asp Ala Val Asp Lys Tyr Leu  
 290 295 300  
 Glu Thr Pro Gly Asp Glu Asn Glu His Ala His Phe Gln Lys Ala Lys  
 305 310 315 320  
 Glu Arg Leu Glu Ala Lys His Arg Glu Arg Met Ser Gln Val Met Arg  
 325 330 335  
 Glu Trp Glu Glu Ala Glu Arg Gln Ala Lys Asn Leu Pro Lys Ala Asp  
 340 345 350  
 Lys Lys Ala Val Ile Gln His Phe Gln Glu Lys Val Glu Ser Leu Glu  
 355 360 365  
 Gln Glu Ala Ala Asn Glu Arg Gln Gln Leu Val Glu Thr His Met Ala  
 370 375 380  
 Arg Val Glu Ala Met Leu Asn Asp Arg Arg Arg Leu Ala Leu Glu Asn  
 385 390 395 400  
 Tyr Ile Thr Ala Leu Gln Ala Val Pro Pro Arg Pro Arg His Val Phe  
 405 410 415  
 Asn Met Leu Lys Lys Tyr Val Arg Ala Glu Gln Lys Asp Arg Gln His  
 420 425 430  
 Thr Leu Lys His Phe Glu His Val Arg Met Val Asp Pro Lys Lys Ala  
 435 440 445  
 Ala Gln Ile Arg Ser Gln Val Met Thr His Leu Arg Val Ile Tyr Glu  
 450 455 460  
 Arg Met Asn Gln Ser Leu Ser Leu Leu Tyr Asn Val Pro Ala Val Ala  
 465 470 475 480  
 Glu Glu Ile Gln Asp Glu Val Asp Glu Leu Leu Gln Lys Glu Gln Asn  
 485 490 495  
 Tyr Ser Asp Asp Val Leu Ala Asn Met Ile Ser Glu Pro Arg Ile Ser  
 500 505 510  
 Tyr Gly Asn Asp Ala Leu Met Pro Ser Leu Thr Glu Thr Lys Thr Thr  
 515 520 525  
 Val Glu Leu Leu Pro Val Asn Gly Glu Phe Ser Leu Asp Asp Leu Gln

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| 530                                                                                | 535  | 540 |
|------------------------------------------------------------------------------------|------|-----|
| Pro Trp His Pro Phe Gly Val Asp Ser Val Pro Ala Asn Thr Glu Asn<br>545 550 555 560 |      |     |
| Glu Val Glu Pro Val Asp Ala Arg Pro Ala Ala Asp Arg Gly Leu Thr<br>565 570 575     |      |     |
| Thr Arg Pro Gly Ser Gly Leu Thr Asn Ile Lys Thr Glu Glu Ile Ser<br>580 585 590     |      |     |
| Glu Val Lys Met Asp Ala Glu Phe Arg His Asp Ser Gly Tyr Glu Val<br>595 600 605     |      |     |
| His His Gln Lys Leu Val Phe Phe Ala Glu Asp Val Gly Ser Asn Lys<br>610 615 620     |      |     |
| Gly Ala Ile Ile Gly Leu Met Val Gly Gly Val Val Ile Ala Thr Val<br>625 630 635 640 |      |     |
| Ile Val Ile Thr Leu Val Met Leu Lys Lys Lys Gln Tyr Thr Ser Ile<br>645 650 655     |      |     |
| His His Gly Val Val Glu Val Asp Ala Ala Val Thr Pro Glu Glu Arg<br>660 665 670     |      |     |
| His Leu Ser Lys Met Gln Gln Asn Gly Tyr Glu Asn Pro Thr Tyr Lys<br>675 680 685     |      |     |
| Phe Phe Glu Gln Met Gln Asn<br>690 695                                             |      |     |
| <210> SEQ ID NO 22                                                                 |      |     |
| <211> LENGTH: 1208                                                                 |      |     |
| <212> TYPE: DNA                                                                    |      |     |
| <213> ORGANISM: Homo Sapiens                                                       |      |     |
| <400> SEQUENCE: 22                                                                 |      |     |
| agagaggggg cgagcgaccg agcgccgcga cgcggaagtg aggtgcgtgc gggctgcagc                  | 60   |     |
| gcagaccccc gcccgcccc tccgagagcg tccctggcgc tccctcacgc cttgccttca                   | 120  |     |
| agccttctgc ctttccaccc tcgtgagcgg agaactggga gtggccattc gacgacaggt                  | 180  |     |
| tagcggggtt gcctcccaact ccccgagcct cgcgtcgccg gctcacagcg gcctcctctg                 | 240  |     |
| gggacagtcc ccccggggtg ccgcctccgc ccttctctgt cgctcctttt ccttcttctt                  | 300  |     |
| tctattataa tattatttgg gaattgttta aatttttttt ttaaaaaaaaa gagagagggc                 | 360  |     |
| gggaggagtc ggagttgtgg agaagcagag ggactcagtg tgggtgaaag gaattcatta                  | 420  |     |
| gccatggatg tattcatgaa aggactttca aaggccaagg agggagttgt ggctgctgct                  | 480  |     |
| gagaaaacca aacagggtgt ggcagaagca gcaggaaaga caaaagaggg tggtctctat                  | 540  |     |
| gtaggctcca aaaccaagga gggagtgtg catggtgtgg caacagtggc tgagaagacc                   | 600  |     |
| aaagagcaag tgacaaatgt tggaggagca gtggtgacgg gtgtgacagc agtagcccag                  | 660  |     |
| aagacagtgg agggagcagg gagcattgca gcagccactg gctttgtcaa aaaggaccag                  | 720  |     |
| ttgggcaaga atgaagaagg agccccacag gaaggaattc tggaagatat gcctgtggat                  | 780  |     |
| cctgacaatg aggcattatga aatgccttct gaggaagggt atcaagacta cgaacctgaa                 | 840  |     |
| gcctaagaaa tatcttttgc cccagtttct tgagatctgc tgacagatgt tccatcctgt                  | 900  |     |
| acaagtgtct agttccaatg tgcccagtca tgacatttct caaagttttt acagtgtatc                  | 960  |     |
| tcgaagtctt ccatcagcag tgattgaagt atctgtacct gccccactc agcatttcgg                   | 1020 |     |
| tgcttccctt tcaactgaagt gaatacatgg tagcagggtc tttgtgtgct gtggattttg                 | 1080 |     |
| tggtttcaat ctacgatgtt aaaacaaatt aaaaacacct aagtgtactac cacttatttc                 | 1140 |     |
| taaatcctca ctattttttg ttgctgttga aaaaaaaaa aaaaaaaaa aaaaaaaaa                     | 1200 |     |

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aaaaaaaa

1208

<210> SEQ ID NO 23  
 <211> LENGTH: 140  
 <212> TYPE: PRT  
 <213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 23

Met Asp Val Phe Met Lys Gly Leu Ser Lys Ala Lys Glu Gly Val Val  
 1 5 10 15

Ala Ala Ala Glu Lys Thr Lys Gln Gly Val Ala Glu Ala Ala Gly Lys  
 20 25 30

Thr Lys Glu Gly Val Leu Tyr Val Gly Ser Lys Thr Lys Glu Gly Val  
 35 40 45

Val His Gly Val Ala Thr Val Ala Glu Lys Thr Lys Glu Gln Val Thr  
 50 55 60

Asn Val Gly Gly Ala Val Val Thr Gly Val Thr Ala Val Ala Gln Lys  
 65 70 75 80

Thr Val Glu Gly Ala Gly Ser Ile Ala Ala Ala Thr Gly Phe Val Lys  
 85 90 95

Lys Asp Gln Leu Gly Lys Asn Glu Glu Gly Ala Pro Gln Glu Gly Ile  
 100 105 110

Leu Glu Asp Met Pro Val Asp Pro Asp Asn Glu Ala Tyr Glu Met Pro  
 115 120 125

Ser Glu Glu Gly Tyr Gln Asp Tyr Glu Pro Glu Ala  
 130 135 140

<210> SEQ ID NO 24  
 <211> LENGTH: 982  
 <212> TYPE: DNA  
 <213> ORGANISM: Porcine

<400> SEQUENCE: 24

cagtcctgtta gggggaggag cttattttctc cattccggtg tgatccagga acagctgttt 60  
 tccctccagc tctgaaagtg tggggtaaag gaattcatta gccatggatg tattcatgaa 120  
 aggactttca aaagccaagg agggagtcgt ggctgctgct gaaaaaacca aacagggtgt 180  
 ggcagaagca gcgggaaaga caaaagaggg tgtgctctat gtaggatcca aaaccaagga 240  
 aggagtgggt catggtgtga caacagtggc tgagaagacc aaagagcaag tgacaaatgt 300  
 tggagaggca gtggtgacag gggtgacagc ggtagcacag aagacagtgg aaggagcagg 360  
 gagcattgca gctgccactg gctttggcaa aaaggatcag ctgggcaaga atgaagaagg 420  
 agccccccag gagggaaatc tggaagatat gcctgtggat cctgacaatg aagcttatga 480  
 aatgccttcc gaggaagggt atcaggacta tgaaccgaa gcctaagggg tatctttgct 540  
 cccagtttcc tgagatctgc tgacagacgt gccatcctgt ccaagtgtccc cgttcccacc 600  
 tgcccagtcg tgaccttctc tcaacgcttt cacagtgtct tttgaagtct tccatgagca 660  
 gtgactggag tatctgtacc cgccccacct cgggtccggt gcttccctct cactgaatat 720  
 atggtagcag ggtcttgtgt gctgtggctg ttgtggcttc gaacctaaaa tgtttaatga 780  
 aaaacaccta agtgactacc acttattttc aaatctattt tttgttgctg ttgagaaatt 840  
 gtgagtgatt tactctccta agatttaaaa gtgtcttttc aggattccgt cgaagaataa 900  
 tgatgtatgg cgaaatttgt taatatatac aatacttaaa catgtgagca tggaactatg 960  
 cacctataaa tattaactat ag 982

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<210> SEQ ID NO 25  
 <211> LENGTH: 140  
 <212> TYPE: PRT  
 <213> ORGANISM: Porcine

<400> SEQUENCE: 25

```
Met Asp Val Phe Met Lys Gly Leu Ser Lys Ala Lys Glu Gly Val Val
 1           5           10           15
Ala Ala Ala Glu Lys Thr Lys Gln Gly Val Ala Glu Ala Ala Gly Lys
      20           25           30
Thr Lys Glu Gly Val Leu Tyr Val Gly Ser Lys Thr Lys Glu Gly Val
      35           40           45
Val His Gly Val Thr Thr Val Ala Glu Lys Thr Lys Glu Gln Val Thr
      50           55           60
Asn Val Gly Glu Ala Val Val Thr Gly Val Thr Ala Val Ala Gln Lys
65           70           75           80
Thr Val Glu Gly Ala Gly Ser Ile Ala Ala Ala Thr Gly Phe Gly Lys
      85           90           95
Lys Asp Gln Leu Gly Lys Asn Glu Glu Gly Ala Pro Gln Glu Gly Ile
      100          105          110
Leu Glu Asp Met Pro Val Asp Pro Asp Asn Glu Ala Tyr Glu Met Pro
      115          120          125
Ser Glu Glu Gly Tyr Gln Asp Tyr Glu Pro Glu Ala
      130          135          140
```

<210> SEQ ID NO 26  
 <211> LENGTH: 982  
 <212> TYPE: DNA  
 <213> ORGANISM: Porcine

<400> SEQUENCE: 26

```

cagtcctgtta gggggaggag cttattttctc cattccggtg tgatccagga acagctgttt      60
tccctccagc tctgaaagtg tggggtaaaag gaattcatta gccatggatg tattcatgaa      120
aggactttca aaagccaagg agggagtcgt ggctgctgct gaaaaaacca aacagggtgt      180
ggcagaagca ccgggaaaga caaaagaggg tgtgctctat gtaggatcca aaaccaagga      240
aggagtgggt catggtgtga caacagtggc tgagaagacc aaagagcaag tgacaaatgt      300
tggagaggca gtggtgacag gggtgacagc ggtagcacag aagacagtgg aaggagcagg      360
gagcattgca gctgccactg gctttggcaa aaaggatcag ctgggcaaga atgaagaagg      420
agccccccag gagggaaatc tggaagatat gcctgtggat cctgacaatg aagcttatga      480
aatgccttcc gaggaagggt atcaggacta tgaaccgaa gcctaagggg tatctttgct      540
cccagtttcc tgagatctgc tgacagacgt gccatcctgt ccaagtgtcc cgttcccacc      600
tgcccagtcg tgaccttctc tcaacgcttt cacagtgtct tttgaagtct tccatgagca      660
gtgactggag tatctgtacc cgccccacct cgggtccggt gcttccctct cactgaatat      720
atggtagcag ggtcttgtgt gctgtggctg ttgtggcttc gaacctaaaa tgtttaatga      780
aaaaacaccta agtgactacc acttatttct aaatctattt tttgttgctg ttgagaaatt      840
gtgagtgatt tactctccta agatttaaaa gtgtcttttc aggattccgt cgaagaataa      900
tgatgtatgg cgaaatttgt taatatatac aatacttaaa catgtgagca tggaactatg      960
cacctataaa tattaactat ag                                     982
```

<210> SEQ ID NO 27  
 <211> LENGTH: 140  
 <212> TYPE: PRT

-continued

&lt;213&gt; ORGANISM: Porcine

&lt;400&gt; SEQUENCE: 27

Met Asp Val Phe Met Lys Gly Leu Ser Lys Ala Lys Glu Gly Val Val  
 1 5 10 15  
 Ala Ala Ala Glu Lys Thr Lys Gln Gly Val Ala Glu Ala Pro Gly Lys  
 20 25 30  
 Thr Lys Glu Gly Val Leu Tyr Val Gly Ser Lys Thr Lys Glu Gly Val  
 35 40 45  
 Val His Gly Val Thr Thr Val Ala Glu Lys Thr Lys Glu Gln Val Thr  
 50 55 60  
 Asn Val Gly Glu Ala Val Val Thr Gly Val Thr Ala Val Ala Gln Lys  
 65 70 75 80  
 Thr Val Glu Gly Ala Gly Ser Ile Ala Ala Ala Thr Gly Phe Gly Lys  
 85 90 95  
 Lys Asp Gln Leu Gly Lys Asn Glu Glu Gly Ala Pro Gln Glu Gly Ile  
 100 105 110  
 Leu Glu Asp Met Pro Val Asp Pro Asp Asn Glu Ala Tyr Glu Met Pro  
 115 120 125  
 Ser Glu Glu Gly Tyr Gln Asp Tyr Glu Pro Glu Ala  
 130 135 140

&lt;210&gt; SEQ ID NO 28

&lt;211&gt; LENGTH: 1109

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Homo Sapiens

&lt;400&gt; SEQUENCE: 28

cctgggcggc tccgctagct gtttttcgtc ttccttaggc tatttctgcc gggcgctccg 60  
 cgaagatgca gctcaagccg atggagatca accccgagat gctgaacaaa gtgctgtccc 120  
 ggctgggggt cgccggccag tggcgcttcg tggacgtgct ggggctggaa gaggagtctc 180  
 tgggctcggt gccagcgctt gcctgcgcgc tgetgctgct gtttccctc acggcccagc 240  
 atgagaactt caggaaaaag cagattgaag agctgaaggg acaagaagtt agtcctaaag 300  
 tgtacttcat gaagcagacc attgggaatt cctgtggcac aatcggaatt attcacgcag 360  
 tggccaataa tcaagacaaa ctgggatttg aggatggatc agttctgaaa cagtttcttt 420  
 ctgaaacaga gaaaattccc ctgaagacag agcaaaatgc tttgaaaaga atgaggccat 480  
 acaggcagcc catgatgccg tggcacagga aggccaatgt cgggtagatg acaaggtgaa 540  
 ttccattttt attctgttta acaacgtgga tggccacctc tatgaacttg atggacgaat 600  
 gccttttccg gtgaaccatg gcgccagttc agaggacacc ctgctgaagg acgctgccaa 660  
 ggtctgcaga gaattcacgc agcgtgagca aggagaagtc cgcttctctg ccgtggctct 720  
 ctgcaaggca gcctaagtct ctgtgggagg gactttgctg atttccctc ttccttcaa 780  
 catgaaaata tataccccc catgcagtct aaaatgcttc agtacttggtg aaacacagct 840  
 gttcttctgt tctgcagaca cgccttcccc tcagccacac ccaggcactt aagcacaagc 900  
 agagtgcaca gctgtccact gggccattgt ggtgtgagct tcagatgggtg aagcattctc 960  
 cccagtgtat gtcttgatc cgatatctaa cgctttaaat ggctactttg gtttctgtct 1020  
 gtaagttaag accttgatg tggtttaatt gtttgcctc aaaaggaata aaacttttct 1080  
 gctgataaga taaaaaaaa aaaaaaaaa 1109

&lt;210&gt; SEQ ID NO 29

&lt;211&gt; LENGTH: 223

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&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Homo Sapiens

&lt;400&gt; SEQUENCE: 29

```

Met Gln Leu Lys Pro Met Glu Ile Asn Pro Glu Met Leu Asn Lys Val
1      5      10      15
Leu Ser Arg Leu Gly Val Ala Gly Gln Trp Arg Phe Val Asp Val Leu
20     25     30
Gly Leu Glu Glu Glu Ser Leu Gly Ser Val Pro Ala Pro Ala Cys Ala
35     40     45
Leu Leu Leu Leu Phe Pro Leu Thr Ala Gln His Glu Asn Phe Arg Lys
50     55     60
Lys Gln Ile Glu Glu Leu Lys Gly Gln Glu Val Ser Pro Lys Val Tyr
65     70     75     80
Phe Met Lys Gln Thr Ile Gly Asn Ser Cys Gly Thr Ile Gly Leu Ile
85     90     95
His Ala Val Ala Asn Asn Gln Asp Lys Leu Gly Phe Glu Asp Gly Ser
100    105    110
Val Leu Lys Gln Phe Leu Ser Glu Thr Glu Lys Met Ser Pro Glu Asp
115    120    125
Arg Ala Lys Cys Phe Glu Lys Asn Glu Ala Ile Gln Ala Ala His Asp
130    135    140
Ala Val Ala Gln Glu Gly Gln Cys Arg Val Asp Asp Lys Val Asn Phe
145    150    155    160
His Phe Ile Leu Phe Asn Asn Val Asp Gly His Leu Tyr Glu Leu Asp
165    170    175
Gly Arg Met Pro Phe Pro Val Asn His Gly Ala Ser Ser Glu Asp Thr
180    185    190
Leu Leu Lys Asp Ala Ala Lys Val Cys Arg Glu Phe Thr Glu Arg Glu
195    200    205
Gln Gly Glu Val Arg Phe Ser Ala Val Ala Leu Cys Lys Ala Ala
210    215    220

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&lt;210&gt; SEQ ID NO 30

&lt;211&gt; LENGTH: 9234

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Homo Sapiens

&lt;400&gt; SEQUENCE: 30

```

cgctggctgc gggcggtgag ctgagctcgc ccccggggag ctgtggccgg cgcccctgcc      60
ggttccctga gcagcgggacg ttcattgctgg gagggcggcg ggttggaagc aggtgccacc      120
atggctagtg gcagctgtca ggggtgcgaa gaggacgagg aaactctgaa gaagttgata      180
gtcaggctga acaatgtcca ggaaggaaaa cagatagaaa cgctggtcca aatcctggag      240
gatctgctgg tgttcacgta ctccgagcac gcctccaagt tatttcaagg caaaaatatc      300
catgtgcctc tgttgatcgt cttggactcc tatatgagag tcgcgagtgt gcagcagggtg      360
ggttggtcac ttctgtgcaa attaatagaa gtctgtccag gtacaatgca aagcttaatg      420
ggaccccagg atgttggaat tgattgggaa gtccttggtg ttcaccaatt gattcttaaa      480
atgctaacag ttcataatgc cagtgtaaac ttgtcagtga ttggactgaa gaccttagat      540
ctcctcctaa cttcaggtaa aatcaccttg ctgatattgg atgaagaaag tgatatattc      600
atgttaattt ttgatgccat gcaactcatt ccagccaatg atgaagtcca gaaacttgga      660
tgcaaagctt tacatgtgct gtttgagaga gtctcagagg agcaactgac tgaatttgtt      720
gagaacaaag attatatgat attgttaagt gcgtcaacaa attttaaaga tgaagaggaa      780

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|                                                                   |      |
|-------------------------------------------------------------------|------|
| attgtgcttc atgtgctgca ttgtttacat tccctagcga ttccttgcaa taatgtggaa | 840  |
| gtcctcatga gtggcaatgt cagggtgtat aatattgtgg tggaaactat gaaagcattc | 900  |
| cctatgagtg aaagaattca agaagtgagt tgctgtttgc tccataggct tacattaggt | 960  |
| aattttttca atatcctggt attaaacgaa gtccatgagt ttgtggtgaa agctgtgcag | 1020 |
| cagtaccag agaatgcagc attgcagatc tcagcgcgca gctgtttggc cctcctcact  | 1080 |
| gagactatct tcttaaatca agatttagag gaaaagaatg agaatcaaga gaatgatgat | 1140 |
| gagggggaag aagataaatt gttttggctg gaagcctgtt acaagcatt aacgtggcat  | 1200 |
| agaaagaaca agcacgtgca ggaggccgca tgctgggcac taaataatct ccttatgtac | 1260 |
| caaacagatt tacatgagaa gattggagat gaagatggcc atttcccagc tcatagggaa | 1320 |
| gtgatgctct ccagtctgat gcattcttca tcaaaggaag tttccaggc atctgcgaat  | 1380 |
| gcattgtcaa ctctcttaga acaaaatggt aatttcagaa aaatactgtt atcaaaagga | 1440 |
| atacacctga atgttttgga gttaatgcag aagcatatac attctcctga agtggctgaa | 1500 |
| agtggctgta aaatgctaaa tcattctttt gaaggaagca acacttcctt ggatataatg | 1560 |
| gcagcagtggt tccccaaat actaacagtt atgaaacgtc atgagacatc attaccagt  | 1620 |
| cagctggagg cgcttcgagc tattttacat tttatagtgc ctggcatgcc agaagaatcc | 1680 |
| agggaggata cagaatttca tcataagcta aatatggtta aaaaacagtg tttcaagaat | 1740 |
| gatattcaca aactggtcct agcagctttg aacagggtca ttggaaatcc tgggattcag | 1800 |
| aaatgtggat taaaagtaat ttctcttatt gtacattttc ctgatgcatt agagatgtta | 1860 |
| tccctggaag gtgctatgga ttcagtgtt caccactgc agatgtatcc agatgaccaa   | 1920 |
| gaaatcaggt gtctgggttt aagctttata ggatactga ttacaaagaa gaatgtgttc  | 1980 |
| ataggaactg gacatctgct ggcaaaaatt ctggtttcca gcttataacc atttaaggat | 2040 |
| gttgctgaaa tacagactaa aggatttcag acaatcttag caatcctcaa attgtcagca | 2100 |
| tctttttcta agctgctggt gcatcattca tttgacttag taatattcca tcaaatgtct | 2160 |
| tccaatatca tggaaacaaa ggatcaacag tttctaaacc tctgttgcaa gtgttttgca | 2220 |
| aaagtagcta tggatgatta cttaaaaaat gtgatgctag agagagcgtg tgatcagaat | 2280 |
| aacagcatca tggttgaatg ctgtcttcta ttgggagcag atgccaatca agcaaaggag | 2340 |
| ggatcttctt taatttgcga ggtatgtgag aaagagagca gtcccaaatt ggtggaactc | 2400 |
| ttactgaata gtggatctcg tgaacaagat gtacgaaaag cgttgacgat aagcattggg | 2460 |
| aaaggtgaca gccagatcat cagcttgctc ttaaggaggc tggccctgga tgtggccaac | 2520 |
| aatagcattt gccttgaggg attttgtata ggaaaagttg aacottcttg gcttggctct | 2580 |
| ttatttccag ataagacttc taatttaagg aaacaaacaa atatagcatc tacactagca | 2640 |
| agaatggtga tcagatatca gatgaaaagt gctgtggaag aaggaacagc ctgagcgagc | 2700 |
| gatggaaatt tttctgaaga tgtgctgtct aaatttgatg aatggacctt tattcctgac | 2760 |
| tcttctatgg acagtgtgtt tgctcaaagt gatgacctgg atagtgaagg aagtgaaggc | 2820 |
| tcatttcttg tgaaaaagaa atctaattca attagtgtag gagaatttta ccgagatgcc | 2880 |
| gtattacagc gttgctcacc aaatttgcaa agacattcca attccttggg gccattttt  | 2940 |
| gatcatgaag atttactgaa gcgaaaaaga aaaatattat cttcagatga ttcactcagg | 3000 |
| tcataaaaac ttcaatccca tatgaggcat tcagacagca tttcttctct ggcttctgag | 3060 |
| agagaatata ttacatcact agacctttca gcaaatgaac taagagatat tgatgcccta | 3120 |
| agccagaaat gctgtataag tgttcatttg gagcatcttg aaaagctgga gcttcaccag | 3180 |

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|             |            |             |             |            |             |      |
|-------------|------------|-------------|-------------|------------|-------------|------|
| aatgcactca  | cgagctttcc | acaacagcta  | tgtgaaactc  | tgaagagttt | gacacatttg  | 3240 |
| gacttgacaca | gtaataaatt | tacatcattt  | ccttcttatt  | tgttgaaaat | gagttgtatt  | 3300 |
| gctaattcttg | atgtctctcg | aaatgacatt  | ggaccctcag  | tggttttaga | tectacagtg  | 3360 |
| aaatgtccaa  | ctctgaaaca | gtttaacctg  | tcataatacc  | agctgtcttt | tgtacctgag  | 3420 |
| aacctcactg  | atgtggtaga | gaaactggag  | cagctcattt  | tagaaggaaa | taaaatatca  | 3480 |
| gggatatgct  | cccccttgag | actgaaggaa  | ctgaagattt  | taaaccttag | taagaaccac  | 3540 |
| atttcacccc  | tatcagagaa | ctttcttgag  | gcttgctcta  | aagtggagag | tttcagtgcc  | 3600 |
| agaatgaatt  | ttcttgctgc | tatgccttcc  | ttgcctcctt  | ctatgacaat | cctaaaatta  | 3660 |
| tctcagaaca  | aattttctcg | tattccagaa  | gcaattttta  | atcttccaca | cttgcggtct  | 3720 |
| ttagatatga  | gcagcaatga | tattcagtac  | ctaccaggtc  | cgcacactg  | gaaatctttg  | 3780 |
| aacttaaggg  | aactcttatt | tagccataat  | cagatcagca  | tcttggaact | gagtgaaaaa  | 3840 |
| gcatatttat  | ggtctagagt | agagaaaactg | catctttctc  | acaataaact | gaaagagatt  | 3900 |
| cctcctgaga  | ttggctgtct | tgaaaatctg  | acatctctgg  | atgtcagtta | caacttgga   | 3960 |
| ctaagatcct  | ttcccaatga | aatggggaaa  | ttaagcaaaa  | tatgggatct | tcctttggat  | 4020 |
| gaactgcac   | ttaactttga | ttttaaacat  | ataggatgta  | aagccaaaga | catcataagg  | 4080 |
| ttcttccaac  | agcgattaaa | aaaggctgtg  | ccttataacc  | gaatgaaact | tatgattgtg  | 4140 |
| ggaaatactg  | ggagtggtaa | aaccacctta  | ttgcagcaat  | taatgaaaac | caagaaatca  | 4200 |
| gatcttgga   | tgcaaatgac | cacagttggc  | atagatgtga  | aagactggcc | tatccaaata  | 4260 |
| agagacaaaa  | gaaagagaga | tctcgtccta  | aatgtgtggg  | attttgcagg | tcgtgaggaa  | 4320 |
| ttctatagta  | ctcatcccca | ttttatgacg  | cagcgagcat  | tgtacctgac | tgtctatgac  | 4380 |
| ctcagcaagg  | gacaggtctg | agttgatgcc  | atgaagcctt  | ggctcttcaa | tataaaggct  | 4440 |
| cgcgcttctt  | cttccctgtg | gattctcgtt  | ggcacacatt  | tggatgtttc | tgatgagaag  | 4500 |
| caacgcaaa   | cctgcatgag | taaaatcacc  | aaggaactcc  | tgaataagcg | agggttccct  | 4560 |
| gccatacgag  | attaccactt | tgtgaatgcc  | accgaggaat  | ctgatgcttt | ggcaaaactt  | 4620 |
| cggaaaaacca | tcataaacga | gagccttaat  | ttcaagatcc  | gagatcagct | tgttgttgga  | 4680 |
| cagctgattc  | cagactgcta | tgtagaactt  | gaaaaaatca  | ttttatcgga | gcgtaaaaat  | 4740 |
| gtgccaatg   | aattttccgt | aattgaccgg  | aaacgattat  | tacaactagt | gagagaaaat  | 4800 |
| cagctgcagt  | tagatgaaaa | tgagcttctt  | cacgcagttc  | actttctaaa | tgaatcagga  | 4860 |
| gtccttcttc  | attttcaaga | cccagcactg  | cagttaagtg  | acttgtactt | tgtggaaccc  | 4920 |
| aagtggcttt  | gtaaaatcat | ggcacagatt  | ttgacagtga  | aagtgggaag | ttgtccaaaa  | 4980 |
| caccctaagg  | gcattatttc | gcgtagagat  | gtggaaaaat  | ttctttcaaa | aaaaaggaaa  | 5040 |
| tttccaaaga  | actacatgac | acagtatttt  | aagctcctag  | aaaaattcca | gattgctttg  | 5100 |
| ccaataggag  | aagaatatct | gctggttcca  | agcagtttgt  | ctgaccacag | gcctgtgata  | 5160 |
| gagcttcccc  | attgtgagaa | ctctgaaatt  | atcatccgac  | tatatgaaat | gccttatttt  | 5220 |
| ccaatgggat  | tttggtaaac | attaatcaat  | cgattacttg  | agatttcacc | ttacatgctt  | 5280 |
| tcaggagag   | aacgagcact | tcgccccaac  | agaatgtatt  | ggcgacaagg | catttactta  | 5340 |
| aattggtctc  | ctgaagctta | ttgtctggta  | ggatctgaag  | tcttagacaa | tcattccagag | 5400 |
| agtttcttaa  | aaattacagt | tccttcttgt  | agaaaaggct  | gtattctttt | gggccaagtt  | 5460 |
| gtggaccaca  | ttgattctct | catggaagaa  | tggtttctctg | ggttgctgga | gattgatatt  | 5520 |
| tgtggtgaag  | gagaaactct | gttgaagaaa  | tgggcattat  | atagttttta | tgatggtgaa  | 5580 |

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|                                                                    |      |
|--------------------------------------------------------------------|------|
| gaacatcaaa aaatcttact tgatgacttg atgaagaaag cagaggaagg agatctctta  | 5640 |
| gtaaaccag atcaaccaag gctcaccatt ccaatatctc agattgcccc tgacttgatt   | 5700 |
| ttggctgacc tgctagaaa tattatgttg aataatgatg agttggaatt tgaacaagct   | 5760 |
| ccagagtffc tcctaggtga tggcagtttt ggatcagttt accgagcagc ctatgaagga  | 5820 |
| gaagaagtgg ctgtgaagat ttttaataaa catacatcac tcaggctggt aagacaagag  | 5880 |
| cttgggtgc tttgccacct ccaccacccc agtttgatat ctttgcggc agctgggatt    | 5940 |
| cgccccgga tgttggtgat ggagttagcc tccaagggtt ccttgatcg cctgcttcag    | 6000 |
| caggacaaag ccagcctcac tagaaccta cagcacagga tgcactcca cgtagctgat    | 6060 |
| ggtttgagat acctccactc agccatgatt atataccgag acctgaaacc ccacaatgtg  | 6120 |
| ctgcttttca cactgtatcc caatgtgcc atcattgcaa agattgctga ctacggcatt   | 6180 |
| gctcagtact gctgtagaat ggggataaaa acatcagagg gcacaccagg gtttcgtgca  | 6240 |
| cctgaagtgg ccagaggaaa tgtcatttat aaccaacagg ctgatgttta ttcatttggg  | 6300 |
| ttactactct atgacatttt gacaactgga ggtagaatag tagagggttt gaagtttcca  | 6360 |
| aatgagtttg atgaattaga aatacaagga aaattacctg atccagttaa agaatatggt  | 6420 |
| tgtgccccat ggcttatggt tgagaaatta attaaacagt gtttgaaaga aaatcctcaa  | 6480 |
| gaaaggccta cttctgccca ggtctttgac attttgaatt cagctgaatt agtctgtctg  | 6540 |
| acgagacgca ttttattacc taaaaacgta attgttgaat gcattggtgc tacacatcac  | 6600 |
| aacagcagga atgcaagcat ttggctgggc tgtgggcaca ccgacagagg acagctctca  | 6660 |
| ttcttgact taaatactga aggatacact tctgaggaag ttgctgatag tagaatattg   | 6720 |
| tgcttagcct tgggtgcatt tcctgttgaa aaggaaagct ggattgtgtc tgggacacag  | 6780 |
| tctggctactc tcctggtcat caataccgaa gatgggaaaa agagacatac cctagaaaag | 6840 |
| atgactgatt ctgtcacttg tttgtattgc aattcctttt ccaagcaaag caaacaacaa  | 6900 |
| aattttcttt tgggtggaac cgctgatggc aagttagcaa tttttgaaga taagactgtt  | 6960 |
| aagcttaaag gagctgctcc tttgaagata ctaaatatag gaaatgtcag tactccattg  | 7020 |
| atgtgtttga gtgaatccac aaattcaacg gaaagaaatg taatgtgggg aggatgtggc  | 7080 |
| acaaagattt tctccttttc taatgatttc accattcaga aactcattga gacaagaaca  | 7140 |
| agccaactgt tttcttatgc agctttcagt gattccaaca tcataacagt ggtggtagac  | 7200 |
| actgctctct atattgctaa gcaaaatagc cctgttgtgg aagtgtggga taagaaaact  | 7260 |
| gaaaaactct gtggactaat agactgctg cactttttta gggaggtaat ggtaaaagaa   | 7320 |
| aacaaggaat caaaacacaa aatgtcttat tctgggagag tgaaaacct ctgccttcag   | 7380 |
| aagaacactg ctctttggat aggaactgga ggaggccata ttttactcct ggatctttca  | 7440 |
| actcgtcgac ttatactgtt aatttacaac ttttgtaatt cggtcagagt catgatgaca  | 7500 |
| gcacagctag gaagccttaa aaatgtcatg ctggtattgg gctacaaccg gaaaaatact  | 7560 |
| gaaggctacac aaaagcagaa agagatacaa tcttgcttga ccgtttggga catcaatctt | 7620 |
| ccacatgaag tgcaaaattt agaaaaacac attgaagtga gaaaagaatt agctgaaaaa  | 7680 |
| atgagacgaa catctgttga gtaagagaga aataggaatt gtctttggat aggaaaaata  | 7740 |
| ttctctctct ttgtaaatat ttattttaaa aatgttcaca tggaaagggt actcacattt  | 7800 |
| tttgaaatag ctctgtgtga tgaaggaatg ttattatttt taattttaat atatgtaaaa  | 7860 |
| atacttacca gtaaatgtgt attttaaaga actattttaa acacaatgtt atatttctta  | 7920 |
| taaataccag ttactttcgt tcattaatta atgaaaataa atctgtgaag tacctaattt  | 7980 |

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aagtactcat actaaaattt ataagggcga taattttttg tttcttgtc tgtaatggag 8040
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&lt;210&gt; SEQ ID NO 31

&lt;211&gt; LENGTH: 2505

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Homo Sapiens

&lt;400&gt; SEQUENCE: 31

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Met Ala Ser Gly Ser Cys Gln Gly Cys Glu Glu Asp Glu Glu Thr Leu
1           5           10           15
Lys Lys Leu Ile Val Arg Leu Asn Asn Val Gln Glu Gly Lys Gln Ile
20          25          30
Glu Thr Leu Val Gln Ile Leu Glu Asp Leu Leu Val Phe Thr Tyr Ser
35          40          45
Glu His Ala Ser Lys Leu Phe Gln Gly Lys Asn Ile His Val Pro Leu
50          55          60
Leu Ile Val Leu Asp Ser Tyr Met Arg Val Ala Ser Val Gln Gln Val
65          70          75          80
Gly Trp Ser Leu Leu Cys Lys Leu Ile Glu Val Cys Pro Gly Thr Met
85          90          95
Gln Ser Leu Met Gly Pro Gln Asp Val Gly Asn Asp Trp Glu Val Leu
100         105         110
Gly Val His Gln Leu Ile Leu Lys Met Leu Thr Val His Asn Ala Ser
115         120         125
Val Asn Leu Ser Val Ile Gly Leu Lys Thr Leu Asp Leu Leu Leu Thr
130         135         140
Ser Gly Lys Ile Thr Leu Leu Ile Leu Asp Glu Glu Ser Asp Ile Phe
145         150         155         160

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|     |     |     |     |     |       |     |     |     |     |     |     |     |     |     |     |  |     |
|-----|-----|-----|-----|-----|-------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|-----|
| Met | Leu | Ile | Phe | Asp | Ala   | Met | His | Ser | Phe | Pro | Ala | Asn | Asp | Glu | Val |  |     |
|     |     |     |     | 165 |       |     |     |     | 170 |     |     |     |     |     | 175 |  |     |
| Gln | Lys | Leu | Gly | Cys | Lys   | Ala | Leu | His | Val | Leu | Phe | Glu | Arg | Val | Ser |  |     |
|     |     |     |     | 180 |       |     |     |     | 185 |     |     |     |     |     | 190 |  |     |
| Glu | Glu | Gln | Leu | Thr | Glu   | Phe | Val | Glu | Asn | Lys | Asp | Tyr | Met | Ile | Leu |  |     |
|     |     |     |     | 195 |       |     |     |     | 200 |     |     |     |     |     | 205 |  |     |
| Leu | Ser | Ala | Ser | Thr | Asn   | Phe | Lys | Asp | Glu | Glu | Glu | Ile | Val | Leu | His |  |     |
|     |     |     |     | 210 |       |     |     |     | 215 |     |     |     |     |     | 220 |  |     |
| Val | Leu | His | Cys | Leu | His   | Ser | Leu | Ala | Ile | Pro | Cys | Asn | Asn | Val | Glu |  |     |
|     |     |     |     | 225 |       |     |     |     | 230 |     | 235 |     |     |     |     |  | 240 |
| Val | Leu | Met | Ser | Gly | Asn   | Val | Arg | Cys | Tyr | Asn | Ile | Val | Val | Glu | Ala |  |     |
|     |     |     |     | 245 |       |     |     |     | 250 |     |     |     |     |     | 255 |  |     |
| Met | Lys | Ala | Phe | Pro | Met   | Ser | Glu | Arg | Ile | Gln | Glu | Val | Ser | Cys | Cys |  |     |
|     |     |     |     | 260 |       |     |     |     | 265 |     |     |     |     |     | 270 |  |     |
| Leu | Leu | His | Arg | Leu | Thr   | Leu | Gly | Asn | Phe | Phe | Asn | Ile | Leu | Val | Leu |  |     |
|     |     |     |     | 275 |       |     |     |     | 280 |     |     |     |     |     | 285 |  |     |
| Asn | Glu | Val | His | Glu | Phe   | Val | Val | Lys | Ala | Val | Gln | Gln | Tyr | Pro | Glu |  |     |
|     |     |     |     | 290 |       |     |     |     | 295 |     | 300 |     |     |     |     |  |     |
| Asn | Ala | Ala | Leu | Gln | Ile   | Ser | Ala | Leu | Ser | Cys | Leu | Ala | Leu | Leu | Thr |  |     |
|     |     |     |     | 305 |       |     |     |     | 310 |     | 315 |     |     |     |     |  | 320 |
| Glu | Thr | Ile | Phe | Leu | Asn   | Gln | Asp | Leu | Glu | Glu | Lys | Asn | Glu | Asn | Gln |  |     |
|     |     |     |     | 325 |       |     |     |     | 330 |     |     |     |     |     | 335 |  |     |
| Glu | Asn | Asp | Asp | Glu | Gly   | Glu | Glu | Asp | Lys | Leu | Phe | Trp | Leu | Glu | Ala |  |     |
|     |     |     |     | 340 |       |     |     |     | 345 |     |     |     |     |     | 350 |  |     |
| Cys | Tyr | Lys | Ala | Leu | Thr   | Trp | His | Arg | Lys | Asn | Lys | His | Val | Gln | Glu |  |     |
|     |     |     |     | 355 |       |     |     |     | 360 |     | 365 |     |     |     |     |  |     |
| Ala | Ala | Cys | Trp | Ala | Leu   | Asn | Asn | Leu | Leu | Met | Tyr | Gln | Asn | Ser | Leu |  |     |
|     |     |     |     | 370 |       |     |     |     | 375 |     | 380 |     |     |     |     |  |     |
| His | Glu | Lys | Ile | Gly | Asp   | Glu | Asp | Gly | His | Phe | Pro | Ala | His | Arg | Glu |  |     |
|     |     |     |     | 385 |       |     |     |     | 390 |     | 395 |     |     |     |     |  | 400 |
| Val | Met | Leu | Ser | Met | Leu   | Met | His | Ser | Ser | Ser | Lys | Glu | Val | Phe | Gln |  |     |
|     |     |     |     | 405 |       |     |     |     | 410 |     |     |     |     |     | 415 |  |     |
| Ala | Ser | Ala | Asn | Ala | Leu   | Ser | Thr | Leu | Leu | Glu | Gln | Asn | Val | Asn | Phe |  |     |
|     |     |     |     | 420 |       |     |     |     | 425 |     |     |     |     |     | 430 |  |     |
| Arg | Lys | Ile | Leu | Leu | Ser   | Lys | Gly | Ile | His | Leu | Asn | Val | Leu | Glu | Leu |  |     |
|     |     |     |     | 435 |       |     |     |     | 440 |     |     |     |     |     | 445 |  |     |
| Met | Gln | Lys | His | Ile | His   | Ser | Pro | Glu | Val | Ala | Glu | Ser | Gly | Cys | Lys |  |     |
|     |     |     |     | 450 |       |     |     |     | 455 |     | 460 |     |     |     |     |  |     |
| Met | Leu | Asn | His | Leu | Phe   | Glu | Gly | Ser | Asn | Thr | Ser | Leu | Asp | Ile | Met |  |     |
|     |     |     |     | 465 |       |     |     |     | 470 |     | 475 |     |     |     |     |  | 480 |
| Ala | Ala | Val | Val | Pro | Lys   | Ile | Leu | Thr | Val | Met | Lys | Arg | His | Glu | Thr |  |     |
|     |     |     |     | 485 |       |     |     |     | 490 |     |     |     |     |     | 495 |  |     |
| Ser | Leu | Pro | Val | Gln | Leu   | Glu | Ala | Leu | Arg | Ala | Ile | Leu | His | Phe | Ile |  |     |
|     |     |     |     | 500 |       |     |     |     | 505 |     |     |     |     |     | 510 |  |     |
| Val | Pro | Gly | Met | Pro | Glu   | Glu | Ser | Arg | Glu | Asp | Thr | Glu | Phe | His | His |  |     |
|     |     |     |     | 515 |       |     |     |     | 520 |     |     |     |     |     | 525 |  |     |
| Lys | Leu | Asn | Met | Val | Lys   | Lys | Gln | Cys | Phe | Lys | Asn | Asp | Ile | His | Lys |  |     |
|     |     |     |     | 530 |       |     |     |     | 535 |     | 540 |     |     |     |     |  |     |
| Leu | Val | Leu | Ala | Ala | Leu   | Asn | Arg | Phe | Ile | Gly | Asn | Pro | Gly | Ile | Gln |  |     |
|     |     |     |     | 545 |       |     |     |     | 550 |     | 555 |     |     |     |     |  | 560 |
| Lys | Cys | Gly | Leu | Lys | Val</ |     |     |     |     |     |     |     |     |     |     |  |     |

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| 580 |     |     |     |     |     |     | 585  |     |     |     |     | 590  |     |     |     |  |
|-----|-----|-----|-----|-----|-----|-----|------|-----|-----|-----|-----|------|-----|-----|-----|--|
| Leu | Gln | Met | Tyr | Pro | Asp | Asp | Gln  | Glu | Ile | Gln | Cys | Leu  | Gly | Leu | Ser |  |
| 595 |     |     |     |     |     |     | 600  |     |     |     |     | 605  |     |     |     |  |
| Leu | Ile | Gly | Tyr | Leu | Ile | Thr | Lys  | Lys | Asn | Val | Phe | Ile  | Gly | Thr | Gly |  |
| 610 |     |     |     |     |     |     | 615  |     |     |     |     | 620  |     |     |     |  |
| His | Leu | Leu | Ala | Lys | Ile | Leu | Val  | Ser | Ser | Leu | Tyr | Arg  | Phe | Lys | Asp |  |
| 625 |     |     |     |     |     |     | 630  |     |     |     |     | 635  |     |     |     |  |
| Val | Ala | Glu | Ile | Gln | Thr | Lys | Gly  | Phe | Gln | Thr | Ile | Leu  | Ala | Ile | Leu |  |
| 645 |     |     |     |     |     |     | 650  |     |     |     |     | 655  |     |     |     |  |
| Lys | Leu | Ser | Ala | Ser | Phe | Ser | Lys  | Leu | Leu | Val | His | His  | Ser | Phe | Asp |  |
| 660 |     |     |     |     |     |     | 665  |     |     |     |     | 670  |     |     |     |  |
| Leu | Val | Ile | Phe | His | Gln | Met | Ser  | Ser | Asn | Ile | Met | Glu  | Gln | Lys | Asp |  |
| 675 |     |     |     |     |     |     | 680  |     |     |     |     | 685  |     |     |     |  |
| Gln | Gln | Phe | Leu | Asn | Leu | Cys | Cys  | Lys | Cys | Phe | Ala | Lys  | Val | Ala | Met |  |
| 690 |     |     |     |     |     |     | 695  |     |     |     |     | 700  |     |     |     |  |
| Asp | Asp | Tyr | Leu | Lys | Asn | Val | Met  | Leu | Glu | Arg | Ala | Cys  | Asp | Gln | Asn |  |
| 705 |     |     |     |     |     |     | 710  |     |     |     |     | 715  |     |     |     |  |
| Asn | Ser | Ile | Met | Val | Glu | Cys | Leu  | Leu | Leu | Leu | Gly | Ala  | Asp | Ala | Asn |  |
| 725 |     |     |     |     |     |     | 730  |     |     |     |     | 735  |     |     |     |  |
| Gln | Ala | Lys | Glu | Gly | Ser | Ser | Leu  | Ile | Cys | Gln | Val | Cys  | Glu | Lys | Glu |  |
| 740 |     |     |     |     |     |     | 745  |     |     |     |     | 750  |     |     |     |  |
| Ser | Ser | Pro | Lys | Leu | Val | Glu | Leu  | Leu | Leu | Asn | Ser | Gly  | Ser | Arg | Glu |  |
| 755 |     |     |     |     |     |     | 760  |     |     |     |     | 765  |     |     |     |  |
| Gln | Asp | Val | Arg | Lys | Ala | Leu | Thr  | Ile | Ser | Ile | Gly | Lys  | Gly | Asp | Ser |  |
| 770 |     |     |     |     |     |     | 775  |     |     |     |     | 780  |     |     |     |  |
| Gln | Ile | Ile | Ser | Leu | Leu | Leu | Arg  | Arg | Leu | Ala | Leu | Asp  | Val | Ala | Asn |  |
| 785 |     |     |     |     |     |     | 790  |     |     |     |     | 795  |     |     |     |  |
| Asn | Ser | Ile | Cys | Leu | Gly | Gly | Phe  | Cys | Ile | Gly | Lys | Val  | Glu | Pro | Ser |  |
| 805 |     |     |     |     |     |     | 810  |     |     |     |     | 815  |     |     |     |  |
| Trp | Leu | Gly | Pro | Leu | Phe | Pro | Asp  | Lys | Thr | Ser | Asn | Leu  | Arg | Lys | Gln |  |
| 820 |     |     |     |     |     |     | 825  |     |     |     |     | 830  |     |     |     |  |
| Thr | Asn | Ile | Ala | Ser | Thr | Leu | Ala  | Arg | Met | Val | Ile | Arg  | Tyr | Gln | Met |  |
| 835 |     |     |     |     |     |     | 840  |     |     |     |     | 845  |     |     |     |  |
| Lys | Ser | Ala | Val | Glu | Glu | Gly | Thr  | Ala | Ser | Gly | Ser | Asp  | Gly | Asn | Phe |  |
| 850 |     |     |     |     |     |     | 855  |     |     |     |     | 860  |     |     |     |  |
| Ser | Glu | Asp | Val | Leu | Ser | Lys | Phe  | Asp | Glu | Trp | Thr | Phe  | Ile | Pro | Asp |  |
| 865 |     |     |     |     |     |     | 870  |     |     |     |     | 875  |     |     |     |  |
| Ser | Ser | Met | Asp | Ser | Val | Phe | Ala  | Gln | Ser | Asp | Asp | Leu  | Asp | Ser | Glu |  |
| 885 |     |     |     |     |     |     | 890  |     |     |     |     | 895  |     |     |     |  |
| Gly | Ser | Glu | Gly | Ser | Phe | Leu | Val  | Lys | Lys | Lys | Ser | Asn  | Ser | Ile | Ser |  |
| 900 |     |     |     |     |     |     | 905  |     |     |     |     | 910  |     |     |     |  |
| Val | Gly | Glu | Phe | Tyr | Arg | Asp | Ala  | Val | Leu | Gln | Arg | Cys  | Ser | Pro | Asn |  |
| 915 |     |     |     |     |     |     | 920  |     |     |     |     | 925  |     |     |     |  |
| Leu | Gln | Arg | His | Ser | Asn | Ser | Leu  | Gly | Pro | Ile | Phe | Asp  | His | Glu | Asp |  |
| 930 |     |     |     |     |     |     | 935  |     |     |     |     | 940  |     |     |     |  |
| Leu | Leu | Lys | Arg | Lys | Arg | Lys | Ile  | Leu | Ser | Ser | Asp | Asp  | Ser | Leu | Arg |  |
| 945 |     |     |     |     |     |     | 950  |     |     |     |     | 955  |     |     |     |  |
| Ser | Ser | Lys | Leu | Gln | Ser | His | Met  | Arg | His | Ser | Asp | Ser  | Ile | Ser | Ser |  |
| 965 |     |     |     |     |     |     | 970  |     |     |     |     | 975  |     |     |     |  |
| Leu | Ala | Ser | Glu | Arg | Glu | Tyr | Ile  | Thr | Ser | Leu | Asp | Leu  | Ser | Ala | Asn |  |
| 980 |     |     |     |     |     |     | 985  |     |     |     |     | 990  |     |     |     |  |
| Glu | Leu | Arg | Asp | Ile | Asp | Ala | Leu  | Ser | Gln | Lys | Cys | Cys  | Ile | Ser | Val |  |
| 995 |     |     |     |     |     |     | 1000 |     |     |     |     | 1005 |     |     |     |  |

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|         |         |         |      |         |         |      |         |     |  |
|---------|---------|---------|------|---------|---------|------|---------|-----|--|
| His Leu | Glu His | Leu Glu | Lys  | Leu Glu | Leu His | Gln  | Asn Ala | Leu |  |
| 1010    |         |         | 1015 |         |         | 1020 |         |     |  |
| Thr Ser | Phe Pro | Gln Gln | Leu  | Cys Glu | Thr Leu | Lys  | Ser Leu | Thr |  |
| 1025    |         |         | 1030 |         |         | 1035 |         |     |  |
| His Leu | Asp Leu | His Ser | Asn  | Lys Phe | Thr Ser | Phe  | Pro Ser | Tyr |  |
| 1040    |         |         | 1045 |         |         | 1050 |         |     |  |
| Leu Leu | Lys Met | Ser Cys | Ile  | Ala Asn | Leu Asp | Val  | Ser Arg | Asn |  |
| 1055    |         |         | 1060 |         |         | 1065 |         |     |  |
| Asp Ile | Gly Pro | Ser Val | Val  | Leu Asp | Pro Thr | Val  | Lys Cys | Pro |  |
| 1070    |         |         | 1075 |         |         | 1080 |         |     |  |
| Thr Leu | Lys Gln | Phe Asn | Leu  | Ser Tyr | Asn Gln | Leu  | Ser Phe | Val |  |
| 1085    |         |         | 1090 |         |         | 1095 |         |     |  |
| Pro Glu | Asn Leu | Thr Asp | Val  | Val Glu | Lys Leu | Glu  | Gln Leu | Ile |  |
| 1100    |         |         | 1105 |         |         | 1110 |         |     |  |
| Leu Glu | Gly Asn | Lys Ile | Ser  | Gly Ile | Cys Ser | Pro  | Leu Arg | Leu |  |
| 1115    |         |         | 1120 |         |         | 1125 |         |     |  |
| Lys Glu | Leu Lys | Ile Leu | Asn  | Leu Ser | Lys Asn | His  | Ile Ser | Ser |  |
| 1130    |         |         | 1135 |         |         | 1140 |         |     |  |
| Leu Ser | Glu Asn | Phe Leu | Glu  | Ala Cys | Pro Lys | Val  | Glu Ser | Phe |  |
| 1145    |         |         | 1150 |         |         | 1155 |         |     |  |
| Ser Ala | Arg Met | Asn Phe | Leu  | Ala Ala | Met Pro | Phe  | Leu Pro | Pro |  |
| 1160    |         |         | 1165 |         |         | 1170 |         |     |  |
| Ser Met | Thr Ile | Leu Lys | Leu  | Ser Gln | Asn Lys | Phe  | Ser Cys | Ile |  |
| 1175    |         |         | 1180 |         |         | 1185 |         |     |  |
| Pro Glu | Ala Ile | Leu Asn | Leu  | Pro His | Leu Arg | Ser  | Leu Asp | Met |  |
| 1190    |         |         | 1195 |         |         | 1200 |         |     |  |
| Ser Ser | Asn Asp | Ile Gln | Tyr  | Leu Pro | Gly Pro | Ala  | His Trp | Lys |  |
| 1205    |         |         | 1210 |         |         | 1215 |         |     |  |
| Ser Leu | Asn Leu | Arg Glu | Leu  | Leu Phe | Ser His | Asn  | Gln Ile | Ser |  |
| 1220    |         |         | 1225 |         |         | 1230 |         |     |  |
| Ile Leu | Asp Leu | Ser Glu | Lys  | Ala Tyr | Leu Trp | Ser  | Arg Val | Glu |  |
| 1235    |         |         | 1240 |         |         | 1245 |         |     |  |
| Lys Leu | His Leu | Ser His | Asn  | Lys Leu | Lys Glu | Ile  | Pro Pro | Glu |  |
| 1250    |         |         | 1255 |         |         | 1260 |         |     |  |
| Ile Gly | Cys Leu | Glu Asn | Leu  | Thr Ser | Leu Asp | Val  | Ser Tyr | Asn |  |
| 1265    |         |         | 1270 |         |         | 1275 |         |     |  |
| Leu Glu | Leu Arg | Ser Phe | Pro  | Asn Glu | Met Gly | Lys  | Leu Ser | Lys |  |
| 1280    |         |         | 1285 |         |         | 1290 |         |     |  |
| Ile Trp | Asp Leu | Pro Leu | Asp  | Glu Leu | His Leu | Asn  | Phe Asp | Phe |  |
| 1295    |         |         | 1300 |         |         | 1305 |         |     |  |
| Lys His | Ile Gly | Cys Lys | Ala  | Lys Asp | Ile Ile | Arg  | Phe Leu | Gln |  |
| 1310    |         |         | 1315 |         |         | 1320 |         |     |  |
| Gln Arg | Leu Lys | Lys Ala | Val  | Pro Tyr | Asn Arg | Met  | Lys Leu | Met |  |
| 1325    |         |         | 1330 |         |         | 1335 |         |     |  |
| Ile Val | Gly Asn | Thr Gly | Ser  | Gly Lys | Thr Thr | Leu  | Leu Gln | Gln |  |
| 1340    |         |         | 1345 |         |         | 1350 |         |     |  |
| Leu Met | Lys Thr | Lys Lys | Ser  | Asp Leu | Gly Met | Gln  | Ser Ala | Thr |  |
| 1355    |         |         | 1360 |         |         | 1365 |         |     |  |
| Val Gly | Ile Asp | Val Lys | Asp  | Trp Pro | Ile Gln | Ile  | Arg Asp | Lys |  |
| 1370    |         |         | 1375 |         |         | 1380 |         |     |  |
| Arg Lys | Arg Asp | Leu Val | Leu  | Asn Val | Trp Asp | Phe  | Ala Gly | Arg |  |
| 1385    |         |         | 1390 |         |         | 1395 |         |     |  |
| Glu Glu | Phe Tyr | Ser Thr | His  | Pro His | Phe Met | Thr  | Gln Arg | Ala |  |
| 1400    |         |         | 1405 |         |         | 1410 |         |     |  |

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|                 |                             |                             |             |
|-----------------|-----------------------------|-----------------------------|-------------|
| Leu Tyr<br>1415 | Leu Ala Val Tyr Asp<br>1420 | Leu Ser Lys Gly Gln<br>1425 | Ala Glu Val |
| Asp Ala<br>1430 | Met Lys Pro Trp Leu<br>1435 | Phe Asn Ile Lys Ala<br>1440 | Arg Ala Ser |
| Ser Ser<br>1445 | Pro Val Ile Leu Val<br>1450 | Gly Thr His Leu Asp<br>1455 | Val Ser Asp |
| Glu Lys<br>1460 | Gln Arg Lys Ala Cys<br>1465 | Met Ser Lys Ile Thr<br>1470 | Lys Glu Leu |
| Leu Asn<br>1475 | Lys Arg Gly Phe Pro<br>1480 | Ala Ile Arg Asp Tyr<br>1485 | His Phe Val |
| Asn Ala<br>1490 | Thr Glu Glu Ser Asp<br>1495 | Ala Leu Ala Lys Leu<br>1500 | Arg Lys Thr |
| Ile Ile<br>1505 | Asn Glu Ser Leu Asn<br>1510 | Phe Lys Ile Arg Asp<br>1515 | Gln Leu Val |
| Val Gly<br>1520 | Gln Leu Ile Pro Asp<br>1525 | Cys Tyr Val Glu Leu<br>1530 | Glu Lys Ile |
| Ile Leu<br>1535 | Ser Glu Arg Lys Asn<br>1540 | Val Pro Ile Glu Phe<br>1545 | Pro Val Ile |
| Asp Arg<br>1550 | Lys Arg Leu Leu Gln<br>1555 | Leu Val Arg Glu Asn<br>1560 | Gln Leu Gln |
| Leu Asp<br>1565 | Glu Asn Glu Leu Pro<br>1570 | His Ala Val His Phe<br>1575 | Leu Asn Glu |
| Ser Gly<br>1580 | Val Leu Leu His Phe<br>1585 | Gln Asp Pro Ala Leu<br>1590 | Gln Leu Ser |
| Asp Leu<br>1595 | Tyr Phe Val Glu Pro<br>1600 | Lys Trp Leu Cys Lys<br>1605 | Ile Met Ala |
| Gln Ile<br>1610 | Leu Thr Val Lys Val<br>1615 | Glu Gly Cys Pro Lys<br>1620 | His Pro Lys |
| Gly Ile<br>1625 | Ile Ser Arg Arg Asp<br>1630 | Val Glu Lys Phe Leu<br>1635 | Ser Lys Lys |
| Arg Lys<br>1640 | Phe Pro Lys Asn Tyr<br>1645 | Met Ser Gln Tyr Phe<br>1650 | Lys Leu Leu |
| Glu Lys<br>1655 | Phe Gln Ile Ala Leu<br>1660 | Pro Ile Gly Glu Glu<br>1665 | Tyr Leu Leu |
| Val Pro<br>1670 | Ser Ser Leu Ser Asp<br>1675 | His Arg Pro Val Ile<br>1680 | Glu Leu Pro |
| His Cys<br>1685 | Glu Asn Ser Glu Ile<br>1690 | Ile Ile Arg Leu Tyr<br>1695 | Glu Met Pro |
| Tyr Phe<br>1700 | Pro Met Gly Phe Trp<br>1705 | Ser Arg Leu Ile Asn<br>1710 | Arg Leu Leu |
| Glu Ile<br>1715 | Ser Pro Tyr Met Leu<br>1720 | Ser Gly Arg Glu Arg<br>1725 | Ala Leu Arg |
| Pro Asn<br>1730 | Arg Met Tyr Trp Arg<br>1735 | Gln Gly Ile Tyr Leu<br>1740 | Asn Trp Ser |
| Pro Glu<br>1745 | Ala Tyr Cys Leu Val<br>1750 | Gly Ser Glu Val Leu<br>1755 | Asp Asn His |
| Pro Glu<br>1760 | Ser Phe Leu Lys Ile<br>1765 | Thr Val Pro Ser Cys<br>1770 | Arg Lys Gly |
| Cys Ile<br>1775 | Leu Leu Gly Gln Val<br>1780 | Val Asp His Ile Asp<br>1785 | Ser Leu Met |
| Glu Glu<br>1790 | Trp Phe Pro Gly Leu<br>1795 | Leu Glu Ile Asp Ile<br>1800 | Cys Gly Glu |
| Gly Glu         | Thr Leu Leu Lys Lys         | Trp Ala Leu Tyr Ser         | Phe Asn Asp |

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| 1805                            | 1810                        | 1815                    |
|---------------------------------|-----------------------------|-------------------------|
| Gly Glu Glu His Gln Lys<br>1820 | Ile Leu Leu Asp Asp<br>1825 | Leu Met Lys Lys<br>1830 |
| Ala Glu Glu Gly Asp Leu<br>1835 | Leu Val Asn Pro Asp<br>1840 | Gln Pro Arg Leu<br>1845 |
| Thr Ile Pro Ile Ser Gln<br>1850 | Ile Ala Pro Asp Leu<br>1855 | Ile Leu Ala Asp<br>1860 |
| Leu Pro Arg Asn Ile Met<br>1865 | Leu Asn Asn Asp Glu<br>1870 | Leu Glu Phe Glu<br>1875 |
| Gln Ala Pro Glu Phe Leu<br>1880 | Leu Gly Asp Gly Ser<br>1885 | Phe Gly Ser Val<br>1890 |
| Tyr Arg Ala Ala Tyr Glu<br>1895 | Gly Glu Glu Val Ala<br>1900 | Val Lys Ile Phe<br>1905 |
| Asn Lys His Thr Ser Leu<br>1910 | Arg Leu Leu Arg Gln<br>1915 | Glu Leu Val Val<br>1920 |
| Leu Cys His Leu His His<br>1925 | Pro Ser Leu Ile Ser<br>1930 | Leu Leu Ala Ala<br>1935 |
| Gly Ile Arg Pro Arg Met<br>1940 | Leu Val Met Glu Leu<br>1945 | Ala Ser Lys Gly<br>1950 |
| Ser Leu Asp Arg Leu Leu<br>1955 | Gln Gln Asp Lys Ala<br>1960 | Ser Leu Thr Arg<br>1965 |
| Thr Leu Gln His Arg Ile<br>1970 | Ala Leu His Val Ala<br>1975 | Asp Gly Leu Arg<br>1980 |
| Tyr Leu His Ser Ala Met<br>1985 | Ile Ile Tyr Arg Asp<br>1990 | Leu Lys Pro His<br>1995 |
| Asn Val Leu Leu Phe Thr<br>2000 | Leu Tyr Pro Asn Ala<br>2005 | Ala Ile Ile Ala<br>2010 |
| Lys Ile Ala Asp Tyr Gly<br>2015 | Ile Ala Gln Tyr Cys<br>2020 | Cys Arg Met Gly<br>2025 |
| Ile Lys Thr Ser Glu Gly<br>2030 | Thr Pro Gly Phe Arg<br>2035 | Ala Pro Glu Val<br>2040 |
| Ala Arg Gly Asn Val Ile<br>2045 | Tyr Asn Gln Gln Ala<br>2050 | Asp Val Tyr Ser<br>2055 |
| Phe Gly Leu Leu Leu Tyr<br>2060 | Asp Ile Leu Thr Thr<br>2065 | Gly Gly Arg Ile<br>2070 |
| Val Glu Gly Leu Lys Phe<br>2075 | Pro Asn Glu Phe Asp<br>2080 | Glu Leu Glu Ile<br>2085 |
| Gln Gly Lys Leu Pro Asp<br>2090 | Pro Val Lys Glu Tyr<br>2095 | Gly Cys Ala Pro<br>2100 |
| Trp Pro Met Val Glu Lys<br>2105 | Leu Ile Lys Gln Cys<br>2110 | Leu Lys Glu Asn<br>2115 |
| Pro Gln Glu Arg Pro Thr<br>2120 | Ser Ala Gln Val Phe<br>2125 | Asp Ile Leu Asn<br>2130 |
| Ser Ala Glu Leu Val Cys<br>2135 | Leu Thr Arg Arg Ile<br>2140 | Leu Leu Pro Lys<br>2145 |
| Asn Val Ile Val Glu Cys<br>2150 | Met Val Ala Thr His<br>2155 | His Asn Ser Arg<br>2160 |
| Asn Ala Ser Ile Trp Leu<br>2165 | Gly Cys Gly His Thr<br>2170 | Asp Arg Gly Gln<br>2175 |
| Leu Ser Phe Leu Asp Leu<br>2180 | Asn Thr Glu Gly Tyr<br>2185 | Thr Ser Glu Glu<br>2190 |
| Val Ala Asp Ser Arg Ile<br>2195 | Leu Cys Leu Ala Leu<br>2200 | Val His Leu Pro<br>2205 |

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|         |                 |      |                 |      |             |
|---------|-----------------|------|-----------------|------|-------------|
| Val Glu | Lys Glu Ser Trp | Ile  | Val Ser Gly Thr | Gln  | Ser Gly Thr |
| 2210    |                 | 2215 |                 | 2220 |             |
| Leu Leu | Val Ile Asn Thr | Glu  | Asp Gly Lys Lys | Arg  | His Thr Leu |
| 2225    |                 | 2230 |                 | 2235 |             |
| Glu Lys | Met Thr Asp Ser | Val  | Thr Cys Leu Tyr | Cys  | Asn Ser Phe |
| 2240    |                 | 2245 |                 | 2250 |             |
| Ser Lys | Gln Ser Lys Gln | Lys  | Asn Phe Leu Leu | Val  | Gly Thr Ala |
| 2255    |                 | 2260 |                 | 2265 |             |
| Asp Gly | Lys Leu Ala Ile | Phe  | Glu Asp Lys Thr | Val  | Lys Leu Lys |
| 2270    |                 | 2275 |                 | 2280 |             |
| Gly Ala | Ala Pro Leu Lys | Ile  | Leu Asn Ile Gly | Asn  | Val Ser Thr |
| 2285    |                 | 2290 |                 | 2295 |             |
| Pro Leu | Met Cys Leu Ser | Glu  | Ser Thr Asn Ser | Thr  | Glu Arg Asn |
| 2300    |                 | 2305 |                 | 2310 |             |
| Val Met | Trp Gly Gly Cys | Gly  | Thr Lys Ile Phe | Ser  | Phe Ser Asn |
| 2315    |                 | 2320 |                 | 2325 |             |
| Asp Phe | Thr Ile Gln Lys | Leu  | Ile Glu Thr Arg | Thr  | Ser Gln Leu |
| 2330    |                 | 2335 |                 | 2340 |             |
| Phe Ser | Tyr Ala Ala Phe | Ser  | Asp Ser Asn Ile | Ile  | Thr Val Val |
| 2345    |                 | 2350 |                 | 2355 |             |
| Val Asp | Thr Ala Leu Tyr | Ile  | Ala Lys Gln Asn | Ser  | Pro Val Val |
| 2360    |                 | 2365 |                 | 2370 |             |
| Glu Val | Trp Asp Lys Lys | Thr  | Glu Lys Leu Cys | Gly  | Leu Ile Asp |
| 2375    |                 | 2380 |                 | 2385 |             |
| Cys Val | His Phe Leu Arg | Glu  | Val Met Val Lys | Glu  | Asn Lys Glu |
| 2390    |                 | 2395 |                 | 2400 |             |
| Ser Lys | His Lys Met Ser | Tyr  | Ser Gly Arg Val | Lys  | Thr Leu Cys |
| 2405    |                 | 2410 |                 | 2415 |             |
| Leu Gln | Lys Asn Thr Ala | Leu  | Trp Ile Gly Thr | Gly  | Gly Gly His |
| 2420    |                 | 2425 |                 | 2430 |             |
| Ile Leu | Leu Leu Asp Leu | Ser  | Thr Arg Arg Leu | Ile  | Arg Val Ile |
| 2435    |                 | 2440 |                 | 2445 |             |
| Tyr Asn | Phe Cys Asn Ser | Val  | Arg Val Met Met | Thr  | Ala Gln Leu |
| 2450    |                 | 2455 |                 | 2460 |             |
| Gly Ser | Leu Lys Asn Val | Met  | Leu Val Leu Gly | Tyr  | Asn Arg Lys |
| 2465    |                 | 2470 |                 | 2475 |             |
| Asn Thr | Glu Gly Thr Gln | Lys  | Gln Lys Glu Ile | Gln  | Ser Cys Leu |
| 2480    |                 | 2485 |                 | 2490 |             |
| Thr Val | Trp Asp Ile Asn | Leu  | Pro His Glu Val | Gln  |             |
| 2495    |                 | 2500 |                 | 2505 |             |

&lt;210&gt; SEQ ID NO 32

&lt;211&gt; LENGTH: 3261

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Homo Sapiens

&lt;400&gt; SEQUENCE: 32

|                                                                   |     |
|-------------------------------------------------------------------|-----|
| gccacaagcc tccaccccag ctggtccccc acccaggctg cccagttaa cattcctagt  | 60  |
| cataggacct tgacttctga gaggcctgat tgtcatctgt aaataagggg taggactaaa | 120 |
| gcactcctcc tggaggactg agagatgggc tggaccggag cacttgagtc tgggatatgt | 180 |
| gaccatgcta ctttgtctc cctgtcctgt tcttccccc agcccaaat ccagggtttt    | 240 |
| ccaaagtgtg gttcaagaac cacctgcac tgaatctaga ggtactggat acaacccac   | 300 |
| gtctgggccc ttaccagga cattctacat gagaacgtgg ggggtggggcc ctggctgcac | 360 |

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|            |             |             |             |             |             |      |
|------------|-------------|-------------|-------------|-------------|-------------|------|
| ctgaactgtc | acctggagtc  | aggggtggaag | gtggaagaac  | tgggtcttat  | tctcttctcc  | 420  |
| ccttggtctt | taggggtctgt | ccttctgcag  | actccgttac  | cccaccctaa  | ccatcctgca  | 480  |
| cacccttgga | gcctctggg   | ccaatgcct   | gtcccgc aaa | gggtcttctca | ggcatctcac  | 540  |
| ctctatggga | gggcattttt  | ggccccaga   | accttacacg  | gtgtttatgt  | ggggaagccc  | 600  |
| ctgggaagca | gacagtccta  | gggtgaagct  | gagaggcaga  | gagaagggga  | gacagacaga  | 660  |
| gggtggggct | tcccccttg   | tctccagtgc  | cctttctggg  | gacctcggg   | tcttttcccc  | 720  |
| caccaccccc | ccagcggagc  | ccatcgtggg  | gaggcttaag  | gaggtccgac  | tgcagaggga  | 780  |
| cgacttcgag | attctgaagg  | tgatcggacg  | cggggcggtc  | agcgaggtag  | cggtagtgaa  | 840  |
| gatgaagcag | acggggccagg | tgtatgccat  | gaagatcatg  | aacaagtggg  | acatgctgaa  | 900  |
| gaggggcgag | gtgtcgtgct  | tccgtgagga  | gagggacgtg  | ttggtgaatg  | gggaccggcg  | 960  |
| gtggatcacg | cagctgcact  | tgccttcca   | ggatgagaac  | tacctgtacc  | tggatcatgga | 1020 |
| gtattacgtg | ggcggggacc  | tgctgacact  | gctgagcaag  | tttggggagc  | ggattccggc  | 1080 |
| cgagatggcg | cgttcttacc  | tggcggagat  | tgtcatggcc  | atagactcgg  | tgcaccggct  | 1140 |
| tggctacgtg | cacagggaca  | tcaaacccca  | caacatcctg  | ctggaccgct  | gtggccacat  | 1200 |
| ccgctcgcc  | gacttcggct  | cttgccctca  | gctgcgggca  | gatggaacgg  | tgcggctgct  | 1260 |
| gggtgctgtg | ggcaccacag  | actacctgtc  | ccccgagatc  | ctgcaggctg  | tgggcgggtg  | 1320 |
| gcctgggaca | ggcagctacg  | ggcccagatg  | tgactggtgg  | gcgtgggtg   | tattcgctta  | 1380 |
| tgaatgttc  | tatgggcaga  | cgccttctta  | cgcggattcc  | acggcggaga  | cctatggcaa  | 1440 |
| gatcgtccac | tacaaggagc  | acctctctct  | gccgtggtg   | gacgaagggg  | tccctgagga  | 1500 |
| ggctcgagac | ttcattcagc  | ggttgctgtg  | tcccccgag   | acacggctgg  | gccgggggtg  | 1560 |
| agcaggcgac | ttccggacac  | atcccttctt  | ctttggcctc  | gactgggatg  | gtctccggga  | 1620 |
| cagcgtgccc | ccctttacac  | cggatttctga | aggtgccacc  | gacacatgca  | acttcgactt  | 1680 |
| ggtgaggagc | gggctcactg  | ccatgggtgag | cgggggcggg  | gagacactgt  | cggacattcg  | 1740 |
| ggaaggtgcg | ccgctagggg  | tccacctgcc  | ttttgtgggc  | tactcctact  | cctgcatggc  | 1800 |
| cctcagggac | agtgaaggct  | caggccccac  | acccatggaa  | ctggaggccg  | agcagctgct  | 1860 |
| tgagccacac | gtgcaagcgc  | ccagcctgga  | gccctcggtg  | tccccacagg  | atgaaacagc  | 1920 |
| tgaagtggca | gttccagcgg  | ctgtccctgc  | ggcagaggct  | gaggccgagg  | tgaagctgcg  | 1980 |
| ggagctccag | gaagccctgg  | aggaggaggt  | gctcaccggg  | cagagcctga  | gccgggagat  | 2040 |
| ggaggccatc | cgcacggaca  | accagaactt  | cgcaggtcaa  | ctacgcgagg  | cagaggctcg  | 2100 |
| gaaccgggac | ctagaggcac  | acgtccggca  | gttgccaggag | cggatggagt  | tgctgcaggc  | 2160 |
| agagggagcc | acagctgtca  | cgggggtccc  | cagtccccgg  | gccacggatc  | caccttccca  | 2220 |
| tctagatggc | cccccgcccg  | tggctgtggg  | ccagtgcctg  | ctggtggggc  | caggcccat   | 2280 |
| gcaccgccgc | cacctgctgc  | tccctgccag  | ggctccctagg | cctggcctat  | cggaggcgct  | 2340 |
| tctcctgctc | ctgttcgcgg  | ttgttctgtc  | tgtgcccgc   | gcctggggct  | gcattggggt  | 2400 |
| gggtggccac | gccggccaac  | tcaccgcagt  | ctggcgccgc  | ccaggagccg  | cccgcgtcc   | 2460 |
| ctgaacccta | gaactgtctt  | cgactccggg  | gccccgttgg  | aagactgagt  | gcccggggca  | 2520 |
| cggcacagaa | gccgcgcccc  | ccgctgcca   | gttcacaacc  | gctccgagcg  | tgggtctccg  | 2580 |
| cccagctcca | gtcctgtgat  | ccgggcccgc  | cccctagcgg  | ccggggaggg  | aggggcccgg  | 2640 |
| tccgcggccg | gcgaacgggg  | ctcgaagggt  | ccttgtagcc  | gggaatgctg  | ctgctgctgc  | 2700 |
| tgctgctgct | gctgctgctg  | ctgctgctgc  | tgctgctgct  | gctgctgggg  | ggatcacaga  | 2760 |

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ccatttcttt ctttcggcca ggctgaggcc ctgacgtgga tgggcaaact gcaggcctgg 2820
gaaggcagca agccggggcg tccgtgttcc atcctccacg cacccccacc tatcgttggt 2880
tcgcaaaagt caaagctttc ttgtgcatga cgccctgctc tggggagcgt ctggcgcgat 2940
ctctgctgct ttactcggga aatttgcttt tgccaaaccc gctttttcgg ggatcccgcg 3000
ccccctcct cacttgcgct gctctcggag ccccgccgg ctcgcccg ctcggcggtt 3060
tggatattta ttgacctcgt cctccgactc gctgacaggc tacaggaccc ccaacaaccc 3120
caatccacgt ttggatgca ctgagacccc gacattcctc ggtatttatt gtctgtcccc 3180
acctaggacc cccaccccgg accctcgcga ataaaaggcc ctccatctgc ccaaaaaaaaa 3240
aaaaaaaaa aaaaaaaaaa a 3261

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&lt;210&gt; SEQ ID NO 33

&lt;211&gt; LENGTH: 639

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Homo Sapiens

&lt;400&gt; SEQUENCE: 33

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Met Gly Gly His Phe Trp Pro Pro Glu Pro Tyr Thr Val Phe Met Trp
1      5      10     15
Gly Ser Pro Trp Glu Ala Asp Ser Pro Arg Val Lys Leu Arg Gly Arg
20     25     30
Glu Lys Gly Arg Gln Thr Glu Gly Ala Phe Pro Leu Val Ser Ser
35     40     45
Ala Leu Ser Gly Asp Pro Arg Phe Phe Ser Pro Thr Thr Pro Pro Ala
50     55     60
Glu Pro Ile Val Val Arg Leu Lys Glu Val Arg Leu Gln Arg Asp Asp
65     70     75     80
Phe Glu Ile Leu Lys Val Ile Gly Arg Gly Ala Phe Ser Glu Val Ala
85     90     95
Val Val Lys Met Lys Gln Thr Gly Gln Val Tyr Ala Met Lys Ile Met
100    105    110
Asn Lys Trp Asp Met Leu Lys Arg Gly Glu Val Ser Cys Phe Arg Glu
115    120    125
Glu Arg Asp Val Leu Val Asn Gly Asp Arg Arg Trp Ile Thr Gln Leu
130    135    140
His Phe Ala Phe Gln Asp Glu Asn Tyr Leu Tyr Leu Val Met Glu Tyr
145    150    155    160
Tyr Val Gly Gly Asp Leu Leu Thr Leu Leu Ser Lys Phe Gly Glu Arg
165    170    175
Ile Pro Ala Glu Met Ala Arg Phe Tyr Leu Ala Glu Ile Val Met Ala
180    185    190
Ile Asp Ser Val His Arg Leu Gly Tyr Val His Arg Asp Ile Lys Pro
195    200    205
Asp Asn Ile Leu Leu Asp Arg Cys Gly His Ile Arg Leu Ala Asp Phe
210    215    220
Gly Ser Cys Leu Lys Leu Arg Ala Asp Gly Thr Val Arg Ser Leu Val
225    230    235    240
Ala Val Gly Thr Pro Asp Tyr Leu Ser Pro Glu Ile Leu Gln Ala Val
245    250    255
Gly Gly Gly Pro Gly Thr Gly Ser Tyr Gly Pro Glu Cys Asp Trp Trp
260    265    270
Ala Leu Gly Val Phe Ala Tyr Glu Met Phe Tyr Gly Gln Thr Pro Phe
275    280    285

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Tyr Ala Asp Ser Thr Ala Glu Thr Tyr Gly Lys Ile Val His Tyr Lys  
 290 295 300  
 Glu His Leu Ser Leu Pro Leu Val Asp Glu Gly Val Pro Glu Glu Ala  
 305 310 315 320  
 Arg Asp Phe Ile Gln Arg Leu Leu Cys Pro Pro Glu Thr Arg Leu Gly  
 325 330 335  
 Arg Gly Gly Ala Gly Asp Phe Arg Thr His Pro Phe Phe Phe Gly Leu  
 340 345 350  
 Asp Trp Asp Gly Leu Arg Asp Ser Val Pro Pro Phe Thr Pro Asp Phe  
 355 360 365  
 Glu Gly Ala Thr Asp Thr Cys Asn Phe Asp Leu Val Glu Asp Gly Leu  
 370 375 380  
 Thr Ala Met Val Ser Gly Gly Gly Glu Thr Leu Ser Asp Ile Arg Glu  
 385 390 395 400  
 Gly Ala Pro Leu Gly Val His Leu Pro Phe Val Gly Tyr Ser Tyr Ser  
 405 410 415  
 Cys Met Ala Leu Arg Asp Ser Glu Val Pro Gly Pro Thr Pro Met Glu  
 420 425 430  
 Leu Glu Ala Glu Gln Leu Leu Glu Pro His Val Gln Ala Pro Ser Leu  
 435 440 445  
 Glu Pro Ser Val Ser Pro Gln Asp Glu Thr Ala Glu Val Ala Val Pro  
 450 455 460  
 Ala Ala Val Pro Ala Ala Glu Ala Glu Ala Glu Val Thr Leu Arg Glu  
 465 470 475 480  
 Leu Gln Glu Ala Leu Glu Glu Glu Val Leu Thr Arg Gln Ser Leu Ser  
 485 490 495  
 Arg Glu Met Glu Ala Ile Arg Thr Asp Asn Gln Asn Phe Ala Ser Gln  
 500 505 510  
 Leu Arg Glu Ala Glu Ala Arg Asn Arg Asp Leu Glu Ala His Val Arg  
 515 520 525  
 Gln Leu Gln Glu Arg Met Glu Leu Leu Gln Ala Glu Gly Ala Thr Ala  
 530 535 540  
 Val Thr Gly Val Pro Ser Pro Arg Ala Thr Asp Pro Pro Ser His Leu  
 545 550 555 560  
 Asp Gly Pro Pro Ala Val Ala Val Gly Gln Cys Pro Leu Val Gly Pro  
 565 570 575  
 Gly Pro Met His Arg Arg His Leu Leu Leu Pro Ala Arg Val Pro Arg  
 580 585 590  
 Pro Gly Leu Ser Glu Ala Leu Ser Leu Leu Leu Phe Ala Val Val Leu  
 595 600 605  
 Ser Arg Ala Ala Ala Leu Gly Cys Ile Gly Leu Val Ala His Ala Gly  
 610 615 620  
 Gln Leu Thr Ala Val Trp Arg Arg Pro Gly Ala Ala Arg Ala Pro  
 625 630 635

&lt;210&gt; SEQ ID NO 34

&lt;211&gt; LENGTH: 4362

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Homo Sapiens

&lt;400&gt; SEQUENCE: 34

|                                                                   |     |
|-------------------------------------------------------------------|-----|
| acggcgagcg cggcgggcgg cggtgacgga ggcgccgtg ccagggggcg tgcggcagcg  | 60  |
| cggcggcggc ggcggcggcg gcggcggcgg aggcggcggc ggcggcggcg gcggcggcgg | 120 |
| aggcggcggc ggcggcggcg gcggcggcgg ctgggcctcg agcgcgcgca gccacacctt | 180 |

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|             |             |             |             |             |             |      |
|-------------|-------------|-------------|-------------|-------------|-------------|------|
| cgggggcg    | ctcccgcg    | tagcagggt   | gaagagaaga  | tggaggagct  | ggtggtggaa  | 240  |
| gtgcggggct  | ccaatggcgc  | tttctacaag  | gcatttgtaa  | aggatgttca  | tgaagattca  | 300  |
| ataacagttg  | catttgaaaa  | caactggcag  | cctgataggc  | agattccatt  | tcatgatgtc  | 360  |
| agattccac   | ctcctgtagg  | ttataataaa  | gatataaatg  | aaagtgatga  | agttgaggtg  | 420  |
| tattccagag  | caaatgaaaa  | agagccttgc  | tgttggtggt  | tagctaaagt  | gaggatgata  | 480  |
| aagggtgagt  | tttatgtgat  | agaatatgca  | gcattgtgatg | caacttaca   | tgaattgtc   | 540  |
| acaattgaac  | gtctaagatc  | tgttaatccc  | aacaaacctg  | ccacaaaaga  | tactttccat  | 600  |
| aagatcaagc  | tggatgtgcc  | agaagactta  | cggcaaatgt  | gtgccaaaga  | ggcggcacat  | 660  |
| aaggatttta  | aaaaggcagt  | tgggtgcctt  | tctgtaactt  | atgatccaga  | aaattatcag  | 720  |
| cttgtcattt  | tgtccatcaa  | tgaagtcacc  | tcaaagcgag  | cacatagct   | gattgacatg  | 780  |
| cactttcgga  | gtctgcgcac  | taagttgtct  | ctgataatga  | gaaatgaaga  | agctagtaag  | 840  |
| cagctggaga  | gttcaaggca  | gcttgctcgc  | agatttcatg  | aacagtttat  | cgtaagagaa  | 900  |
| gatctgatgg  | gtctagctat  | tgggtactcat | ggtgctaata  | ttcagcaagc  | tagaaaagta  | 960  |
| cctgggggtca | ctgctattga  | tctagatgaa  | gataacctgca | catttcatat  | ttagggagag  | 1020 |
| gatcaggatg  | cagtgaaaaa  | agctagaagc  | tttctcgaat  | ttgctgaaga  | tgtaatataa  | 1080 |
| gttccaagga  | acttagtagg  | caaagtaata  | ggaaaaaatg  | gaaagctgat  | tcaggagatt  | 1140 |
| gtggacaagt  | caggagtgtg  | gagggtaggg  | attgaggctg  | aaaatgagaa  | aatgtttcca  | 1200 |
| caagaagagg  | aaattatgcc  | accaaattcc  | cttccttcca  | ataattcaag  | ggttgacct   | 1260 |
| aatgccccag  | aagaaaaaaa  | acatttagat  | ataaaggaaa  | acagcaccca  | tttttctcaa  | 1320 |
| cctaacagta  | caaaagtcca  | gaggggtgta  | gtggcttcat  | cagttgtagc  | aggggaatcc  | 1380 |
| cagaaacctg  | aactcaaggc  | ttggcagggt  | atggtaccat  | ttgtttttgt  | gggaacaaag  | 1440 |
| gacagcatcg  | ctaattgccac | tgttcttttg  | gattatcacc  | tgaactat    | aaaggaagta  | 1500 |
| gaccagttgc  | gtttggagag  | attacaaatt  | gatgagcagt  | tgcgacagat  | tggagctagt  | 1560 |
| tctagaccac  | caccaaatcg  | tacagataag  | gaaaaaagct  | atgtgactga  | tgatgggtcaa | 1620 |
| ggaatgggtc  | gaggtagtag  | accttacaga  | aatagggggc  | acggcagacg  | cggtcctgga  | 1680 |
| tatacttcag  | gaactaatc   | tgaagcatca  | aatgcttctg  | aaacagaatc  | tgaccacaga  | 1740 |
| gacgaactca  | gtgattggtc  | attagctcca  | acagagggaag | agagggagag  | cttctgcgc   | 1800 |
| agaggagacg  | gacggcgggc  | tggaggggga  | ggaagaggac  | aaggagggaag | aggacgtgga  | 1860 |
| ggaggcttca  | aaggaaacga  | cgatcactcc  | cgaacagata  | atcgtccacg  | taatccaaga  | 1920 |
| gaggctaaa   | gaagaacaac  | agatggatcc  | cttcagatca  | gagttgactg  | caataatgaa  | 1980 |
| aggagtgtcc  | acactaaaac  | attacagaat  | acctccagtg  | aaggtagtcg  | gctgcgcacg  | 2040 |
| ggtaaagatc  | gtaaccagaa  | gaaagagaag  | ccagacagcg  | tggatggtca  | gcaaccactc  | 2100 |
| gtgaatggag  | taccctaaac  | tgcataatc   | tgaagttata  | tttctatac   | catttccgta  | 2160 |
| attcttattc  | catattagaa  | aactttgtta  | ggccaaagac  | aaatagtagg  | caagatggca  | 2220 |
| cagggcata   | aatgaacaca  | aattatgcta  | agaatttttt  | attttttggt  | attggccata  | 2280 |
| agcaacaatt  | ttcagatttg  | cacaaaaaga  | taccttaaaa  | tttgaaacat  | tgctttttaa  | 2340 |
| actacttagc  | acttcagggc  | agatttttagt | tttattttct  | aaagtactga  | gcagtgatat  | 2400 |
| tctttgttaa  | tttggaccat  | tttctgcat   | tgggtgatca  | ttcaccagta  | cattctcagt  | 2460 |
| ttttcttaat  | atatagcatt  | tatggtaatc  | atattagact  | tctgttttca  | atctcgtata  | 2520 |
| gaagtcttca  | tgaatgcta   | tgtcatttca  | tgtcctgtgt  | cagtttatgt  | tttggccac   | 2580 |

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ttttccagta ttttagtgga ccttgaaatg tgtgtgatgt gacatttgtc attttcatta 2640
gcaaaaaaag ttgtatgatc tgtgcctttt ttatatcttg gcaggtagga atattatatt 2700
tggatgcaga gttcagggaa gataagttgg aaacactaaa tgttaaagat gtagcaaacc 2760
ctgtcaaaca ttagtacttt atagaagaat gcatgccttc catatttttt tccttacata 2820
aacatcaggt taggcagtat aaagaatagg acttgttttt gtttttgttt tgttgcactg 2880
aagtttgata aatagtgtta ttgagagaga tgtgtaattt tctgtatag acaggagaag 2940
aaagaactat ctcatctga gagaggctaa aatgttttca gctaggaaca aatcttcctg 3000
gtcgaaagtt agtaggatat gcctgctctt tggcctgatg accaatttta acttagagct 3060
ttttttttta attttgtctg ccccaagttt tgtgaaattt tcatattttt aatttcaagc 3120
ttattttgga gagataggaa ggtcatttcc atgtatgcat aataatcctg caaagtacag 3180
gtactttgtc taagaaacat tggaagcagg ttaaatgttt tgtaaacctt gaaatatatg 3240
gtctaagtgt taagcagaat tggaaaagac taagatcggg taacaaataa caactttttt 3300
ttcttttttt cttttgtttt ttgaagtgtt ggggttttgt tttgtttttt gagtcttttt 3360
tttttaagtg aaattttatt aggaaaaata tgtgaaggac cttcactcta agatgttata 3420
tttttcttaa aaagtaactc ctagtagggg taccactgaa tctgtacaga gccgtaaaaa 3480
ctgaagttct gcctctgatg tattttgtga gtttgtttct ttgaatttcc attttacagt 3540
tacttttctc tgcatacaaa caagcatata aaatggcaac aaactgcaca tgatttcaca 3600
aatattaaaa agtcttttaa aaagtattgc caaacattaa tgttgatttc tagttattta 3660
ttctgggaat gtatagtatt tgaaaacaga aattgggtacc ttgcacacat catctgtaag 3720
ctgtttgggt ttaaaatact gtagataatt aaccaaggta gaatgacctt gtaatgtaac 3780
tgctcttggg caatattctc tgtacatatt agcgacaaca gattggattt tatgttgaca 3840
tttgttttgt tatagtgcaa tatattttgt atgcaagcag tttcaataaa gtttgatctt 3900
cctctgctaa attgatgttg atgcaatcct tacaaatgat tgcttttaaa attttaagct 3960
aggaaaagaa atctatagaa agtgttctgt tacaaaatgt aactgttacc attggaaatt 4020
tcacgtcata ggaagttagc ctttatctac ccaactttca agaaggttct ttaataaagc 4080
gaaaactcaa ccaaatggta cttttccaca gtgtaccatt aaaatatgca ctagtctctt 4140
tttacaaggc tgtattcagc aagggcctaa cttgcttaaa gtgtaattac taacttctaa 4200
aactgtactt tgattcacat gttttcaaat ggagttggag ttcattcata ttacaatatt 4260
tgtgtgctaa acgtgtatgt ttttcagttc aaagtcatga tgtttttaaa atcttattaa 4320
agtttcaaaa atctgaagat tgtttatcta gatgtaaatt tt 4362

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&lt;210&gt; SEQ ID NO 35

&lt;211&gt; LENGTH: 632

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Homo Sapiens

&lt;400&gt; SEQUENCE: 35

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Met Glu Glu Leu Val Val Glu Val Arg Gly Ser Asn Gly Ala Phe Tyr
1           5           10          15

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Lys Ala Phe Val Lys Asp Val His Glu Asp Ser Ile Thr Val Ala Phe
20          25          30

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Glu Asn Asn Trp Gln Pro Asp Arg Gln Ile Pro Phe His Asp Val Arg
35          40          45

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Phe Pro Pro Pro Val Gly Tyr Asn Lys Asp Ile Asn Glu Ser Asp Glu
50          55          60

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|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Glu | Val | Tyr | Ser | Arg | Ala | Asn | Glu | Lys | Glu | Pro | Cys | Cys | Trp | Trp | 65  | 70  | 75  | 80  |
| Leu | Ala | Lys | Val | Arg | Met | Ile | Lys | Gly | Glu | Phe | Tyr | Val | Ile | Glu | Tyr | 85  | 90  | 95  |     |
| Ala | Ala | Cys | Asp | Ala | Thr | Tyr | Asn | Glu | Ile | Val | Thr | Ile | Glu | Arg | Leu | 100 | 105 | 110 |     |
| Arg | Ser | Val | Asn | Pro | Asn | Lys | Pro | Ala | Thr | Lys | Asp | Thr | Phe | His | Lys | 115 | 120 | 125 |     |
| Ile | Lys | Leu | Asp | Val | Pro | Glu | Asp | Leu | Arg | Gln | Met | Cys | Ala | Lys | Glu | 130 | 135 | 140 |     |
| Ala | Ala | His | Lys | Asp | Phe | Lys | Lys | Ala | Val | Gly | Ala | Phe | Ser | Val | Thr | 145 | 150 | 155 | 160 |
| Tyr | Asp | Pro | Glu | Asn | Tyr | Gln | Leu | Val | Ile | Leu | Ser | Ile | Asn | Glu | Val | 165 | 170 | 175 |     |
| Thr | Ser | Lys | Arg | Ala | His | Met | Leu | Ile | Asp | Met | His | Phe | Arg | Ser | Leu | 180 | 185 | 190 |     |
| Arg | Thr | Lys | Leu | Ser | Leu | Ile | Met | Arg | Asn | Glu | Glu | Ala | Ser | Lys | Gln | 195 | 200 | 205 |     |
| Leu | Glu | Ser | Ser | Arg | Gln | Leu | Ala | Ser | Arg | Phe | His | Glu | Gln | Phe | Ile | 210 | 215 | 220 |     |
| Val | Arg | Glu | Asp | Leu | Met | Gly | Leu | Ala | Ile | Gly | Thr | His | Gly | Ala | Asn | 225 | 230 | 235 | 240 |
| Ile | Gln | Gln | Ala | Arg | Lys | Val | Pro | Gly | Val | Thr | Ala | Ile | Asp | Leu | Asp | 245 | 250 | 255 |     |
| Glu | Asp | Thr | Cys | Thr | Phe | His | Ile | Tyr | Gly | Glu | Asp | Gln | Asp | Ala | Val | 260 | 265 | 270 |     |
| Lys | Lys | Ala | Arg | Ser | Phe | Leu | Glu | Phe | Ala | Glu | Asp | Val | Ile | Gln | Val | 275 | 280 | 285 |     |
| Pro | Arg | Asn | Leu | Val | Gly | Lys | Val | Ile | Gly | Lys | Asn | Gly | Lys | Leu | Ile | 290 | 295 | 300 |     |
| Gln | Glu | Ile | Val | Asp | Lys | Ser | Gly | Val | Val | Arg | Val | Arg | Ile | Glu | Ala | 305 | 310 | 315 | 320 |
| Glu | Asn | Glu | Lys | Asn | Val | Pro | Gln | Glu | Glu | Glu | Ile | Met | Pro | Pro | Asn | 325 | 330 | 335 |     |
| Ser | Leu | Pro | Ser | Asn | Asn | Ser | Arg | Val | Gly | Pro | Asn | Ala | Pro | Glu | Glu | 340 | 345 | 350 |     |
| Lys | Lys | His | Leu | Asp | Ile | Lys | Glu | Asn | Ser | Thr | His | Phe | Ser | Gln | Pro | 355 | 360 | 365 |     |
| Asn | Ser | Thr | Lys | Val | Gln | Arg | Val | Leu | Val | Ala | Ser | Ser | Val | Val | Ala | 370 | 375 | 380 |     |
| Gly | Glu | Ser | Gln | Lys | Pro | Glu | Leu | Lys | Ala | Trp | Gln | Gly | Met | Val | Pro | 385 | 390 | 395 | 400 |
| Phe | Val | Phe | Val | Gly | Thr | Lys | Asp | Ser | Ile | Ala | Asn | Ala | Thr | Val | Leu | 405 | 410 | 415 |     |
| Leu | Asp | Tyr | His | Leu | Asn | Tyr | Leu | Lys | Glu | Val | Asp | Gln | Leu | Arg | Leu | 420 | 425 | 430 |     |
| Glu | Arg | Leu | Gln | Ile | Asp | Glu | Gln | Leu | Arg | Gln | Ile | Gly | Ala | Ser | Ser | 435 | 440 | 445 |     |
| Arg | Pro | Pro | Pro | Asn | Arg | Thr | Asp | Lys | Glu | Lys | Ser | Tyr | Val | Thr | Asp | 450 | 455 | 460 |     |
| Asp | Gly | Gln | Gly | Met | Gly | Arg | Gly | Ser | Arg | Pro | Tyr | Arg | Asn | Arg | Gly | 465 | 470 | 475 | 480 |
| His | Gly | Arg | Arg | Gly | Pro | Gly | Tyr | Thr | Ser | Gly | Thr | Asn | Ser | Glu | Ala | 485 | 490 | 495 |     |

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Ser Asn Ala Ser Glu Thr Glu Ser Asp His Arg Asp Glu Leu Ser Asp  
500 505 510

Trp Ser Leu Ala Pro Thr Glu Glu Glu Arg Glu Ser Phe Leu Arg Arg  
515 520 525

Gly Asp Gly Arg Arg Arg Gly Gly Gly Gly Arg Gly Gln Gly Gly Arg  
530 535 540

Gly Arg Gly Gly Gly Phe Lys Gly Asn Asp Asp His Ser Arg Thr Asp  
545 550 555 560

Asn Arg Pro Arg Asn Pro Arg Glu Ala Lys Gly Arg Thr Thr Asp Gly  
565 570 575

Ser Leu Gln Ile Arg Val Asp Cys Asn Asn Glu Arg Ser Val His Thr  
580 585 590

Lys Thr Leu Gln Asn Thr Ser Ser Glu Gly Ser Arg Leu Arg Thr Gly  
595 600 605

Lys Asp Arg Asn Gln Lys Lys Glu Lys Pro Asp Ser Val Asp Gly Gln  
610 615 620

Gln Pro Leu Val Asn Gly Val Pro  
625 630

&lt;210&gt; SEQ ID NO 36

&lt;211&gt; LENGTH: 3819

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Homo Sapiens

&lt;400&gt; SEQUENCE: 36

|                                                                    |      |
|--------------------------------------------------------------------|------|
| atggatctat tcgacttttt cagagactgg gacttggagc agcagtgta cttgaacaa    | 60   |
| gaccgtagtg cacttaaaaa aagggaatgg gagcggagga atcaagaagt ccagcaagaa  | 120  |
| gacgatctct tttcttcagg ctttgatctt tttggggagc catacaagac aaacaaaggt  | 180  |
| gatgcacttg ccaaccgagt ccagaacacg cttggaaact atgatgaaat gaagaatttg  | 240  |
| ctaactaacc attctaata caaatcaccta gtgggaattc caaagaattc tgtgccccag  | 300  |
| aatcccaaca acaaaaatga accaagcttt tttccagaac aaaagaacag aataattcca  | 360  |
| cctcaccagg ataataccca tccttcagca ccaatgcctc caccttctgt tgtgatactg  | 420  |
| aattcaactc taatacacag caacagaaaa tcaaaacctg agtgggtcacg tgatagtcac | 480  |
| aaccctagca ctgtactggc aagccaggcc agtgggtcacg caaacaagat gcagactttg | 540  |
| acacaggacc agtctcaagc caaactggaa gacttccttg tctaccagc tgaacagccc   | 600  |
| cagattggag aagttgaaga gtcaaaccca tctgcaaagg aagacagtaa ccctaattct  | 660  |
| agtggagaag atgctttcaa agaaatcttt caatccaatt caccggaaga atctgaattc  | 720  |
| gccgtgcaag cgctggggtc tcccctagtg gcttcctctt tattagctcc tagcagtggc  | 780  |
| ctttcagttc aaaacttccc accagggctt tactgcacaa caagcatggg gcagcaaaag  | 840  |
| ccaactgcat acgtcagacc catggatggc caggaccagg caccggacat ctcaccaaca  | 900  |
| ctgaaacctt caattgaatt tgagaacagc tttgggaatc tgtcatttgg aacactcttg  | 960  |
| gatggaaaac ccagtgcagc cagttcaaa actaaactgc caaagttcac catcctccaa   | 1020 |
| acaagtgaag taagccttcc cagtgatcca agctgtgttg aagaaatctt gcgggaatcg  | 1080 |
| cagcatctga cccaggatt caccttaca aagtggaatg acccaaccac cagagcttct    | 1140 |
| acaaagatgc ttgaggatga cctgaagctg agcagtgatg aagatgacct tgagcctgtg  | 1200 |
| aagaccttga ccaactcagt cactgccact gagctctacc aggctgttga aaaggcaaaa  | 1260 |
| cctaggaata atcctgtgaa cccacccttg gccactcccc agccccacc tgcagtgcaa   | 1320 |

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|             |            |             |            |            |             |      |
|-------------|------------|-------------|------------|------------|-------------|------|
| gccagcgggg  | gttctggcag | ctccagcgaa  | tcggagagca | gctctgagtc | ggattcagac  | 1380 |
| actgaaagta  | gcaccactga | cagcgaatct  | aatgaggcac | ctcgtgtggc | aactccagag  | 1440 |
| cctgagccac  | cctcaaccaa | caagtggcaa  | ctggataaat | ggcttaacaa | agtgcacatcc | 1500 |
| cagaacaagt  | cttttatttg | tggccaaaat  | gaaacaccca | tggagactat | ttctctgcct  | 1560 |
| cctccaatca  | tccaaccaat | ggaagtccag  | atgaaagtga | agacgaatgc | cagtcaggtc  | 1620 |
| ccagctgaac  | ccaaagaaag | gcctctcttc  | agtctcatta | gggagaaagc | ccgtccacgg  | 1680 |
| cccactcaga  | aaattccaga | aacaaaggct  | ttgaagcata | agttgtcaac | aactagttag  | 1740 |
| acagtgtctc  | aaaggacaat | tgggaaaaaa  | cagcccaaaa | aagttgagaa | gaacaccagc  | 1800 |
| actgacgagt  | ttacctggcc | caaaccaaat  | attaccagca | gcactcccaa | agaaaaagaa  | 1860 |
| agtggtggagc | ttcatgaccc | accaagaggc  | cgcaacaaag | ccactgcccc | caaaccagcc  | 1920 |
| cctaggaaag  | aaccaagacc | taacatccct  | ttggctcccg | agaagaagaa | gtacagaggg  | 1980 |
| cctggcaaga  | ttgtgccaaa | gtctcgggaa  | ttcattgaaa | cagattcatc | tacatctgac  | 2040 |
| tccaacacag  | atcaggaaga | gaccctgcaa  | atcaaagtcc | tgcctccgtg | cattatttct  | 2100 |
| ggaggttaata | ctgccaaatc | caaggaaaatc | tgtggtgcc  | gcctgaccct | cagcacotta  | 2160 |
| atgagtagca  | gtggcagcaa | caacaactta  | tccatcagta | atgaagagcc | aacattttca  | 2220 |
| cctattcctg  | tcatgcaaac | tgaatcctg   | tcccctctgc | gagatcatga | gaacctgaaa  | 2280 |
| aacctctggg  | tgaagattga | ccttgactta  | ctctctagag | tacctggcca | cagctcactc  | 2340 |
| catgcagcac  | ctgccaaagc | agaccacaag  | gagactgcc  | caaaacccaa | gcgtcagaca  | 2400 |
| gctgtcacag  | ctgtggagaa | accagcccct  | aagggcacaa | gtaagcaca  | gccaatagaa  | 2460 |
| gttgacagaga | agatccctga | gaagaagcag  | cgcttgagg  | aggccacaac | tatctgcttg  | 2520 |
| ctccctcctt  | gcattctacc | agccccccc   | cacaagcctc | ccaacactag | agaaaataat  | 2580 |
| tcatccagga  | gagcaaatag | aagaaaggaa  | gaaaaactat | ttctctctcc | actttcccca  | 2640 |
| ctgccagagg  | accctccacg | ccgcagaaat  | gtcagtggca | ataatggtcc | ctttggtcaa  | 2700 |
| gacaaaaaca  | tcgccatgac | tggacaaatc  | acatctacca | aacctaaag  | aactgaaggc  | 2760 |
| aaattctgtg  | ctactttcaa | agggatatcg  | gtaaatgagg | gagacactcc | aaaaaaggca  | 2820 |
| tcctctgcca  | ccatcactgt | caccaatact  | gctattgcca | ctgctactgt | cactgctact  | 2880 |
| gccattgtca  | ccaccactgt | cacagctact  | gccaccgcca | cggccaccac | cacaactact  | 2940 |
| accactacca  | ttccaccat  | cacctctacc  | atcactactg | gcctcatgga | tagcagtcac  | 3000 |
| ctggagatga  | cgtcctgggc | ggctctgccc  | cttctatcca | gcagcagcac | taatgtccgg  | 3060 |
| agacccaagc  | tcacttttga | tgactcgggt  | cacaatgctg | attattacat | gcaagaagct  | 3120 |
| aagaagctga  | agcacaaagc | tgatgcactg  | ttcgagaaat | ttggcaaagc | tgtgaattat  | 3180 |
| gctgatgccg  | ccctctcctt | cactgaatgt  | ggcaatgcc  | tggaaacgca | ccctctggaa  | 3240 |
| gcaaagtccc  | catacaccat | gtactctgag  | actgtggagc | tcctcaggta | tgcaatgagg  | 3300 |
| ctgaagaact  | ttgcaagtcc | cttggtctcg  | gatggggaca | aaaagctagc | agtactatgc  | 3360 |
| taccgatgtt  | tatcactcct | ctatttgaga  | atgtttaagc | tgaagaagga | ccatgctatg  | 3420 |
| aagtactcca  | gatcactgat | ggaatatattt | aagcaaaatg | cttcaaaagt | cgcacagata  | 3480 |
| ccctctccat  | gggtaagcaa | tggaaagaac  | actccatccc | cagtgtctct | caacaacgtc  | 3540 |
| tcccccatca  | acgcaatggg | gaactgtaac  | aatggcccag | tcaccattcc | ccagcgcatt  | 3600 |
| caccacatgg  | ctgccagcca | cgtcaacatc  | actagcaatg | tgttacgggg | ctatgaacac  | 3660 |
| tgggatatgg  | ccgacaaaat | gacaagagaa  | aacaaagaat | tctttggtga | tctggacacg  | 3720 |

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ctgatggggc ctctgaccca gcacagcagc atgaccaatc ttgtccgcta cgttcgcaa 3780  
 ggactgtgtt ggctgcgcac cgatgcccac ttgtttag 3819

<210> SEQ ID NO 37  
 <211> LENGTH: 1272  
 <212> TYPE: PRT  
 <213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 37

Met Asp Leu Phe Asp Phe Phe Arg Asp Trp Asp Leu Glu Gln Gln Cys  
 1 5 10 15  
 His Tyr Glu Gln Asp Arg Ser Ala Leu Lys Lys Arg Glu Trp Glu Arg  
 20 25 30  
 Arg Asn Gln Glu Val Gln Gln Glu Asp Asp Leu Phe Ser Ser Gly Phe  
 35 40 45  
 Asp Leu Phe Gly Glu Pro Tyr Lys Thr Asn Lys Gly Asp Ala Leu Ala  
 50 55 60  
 Asn Arg Val Gln Asn Thr Leu Gly Asn Tyr Asp Glu Met Lys Asn Leu  
 65 70 75 80  
 Leu Thr Asn His Ser Asn Gln Asn His Leu Val Gly Ile Pro Lys Asn  
 85 90 95  
 Ser Val Pro Gln Asn Pro Asn Asn Lys Asn Glu Pro Ser Phe Phe Pro  
 100 105 110  
 Glu Gln Lys Asn Arg Ile Ile Pro Pro His Gln Asp Asn Thr His Pro  
 115 120 125  
 Ser Ala Pro Met Pro Pro Pro Ser Val Val Ile Leu Asn Ser Thr Leu  
 130 135 140  
 Ile His Ser Asn Arg Lys Ser Lys Pro Glu Trp Ser Arg Asp Ser His  
 145 150 155 160  
 Asn Pro Ser Thr Val Leu Ala Ser Gln Ala Ser Gly Gln Pro Asn Lys  
 165 170 175  
 Met Gln Thr Leu Thr Gln Asp Gln Ser Gln Ala Lys Leu Glu Asp Phe  
 180 185 190  
 Phe Val Tyr Pro Ala Glu Gln Pro Gln Ile Gly Glu Val Glu Glu Ser  
 195 200 205  
 Asn Pro Ser Ala Lys Glu Asp Ser Asn Pro Asn Ser Ser Gly Glu Asp  
 210 215 220  
 Ala Phe Lys Glu Ile Phe Gln Ser Asn Ser Pro Glu Glu Ser Glu Phe  
 225 230 235 240  
 Ala Val Gln Ala Pro Gly Ser Pro Leu Val Ala Ser Ser Leu Leu Ala  
 245 250 255  
 Pro Ser Ser Gly Leu Ser Val Gln Asn Phe Pro Pro Gly Leu Tyr Cys  
 260 265 270  
 Lys Thr Ser Met Gly Gln Gln Lys Pro Thr Ala Tyr Val Arg Pro Met  
 275 280 285  
 Asp Gly Gln Asp Gln Ala Pro Asp Ile Ser Pro Thr Leu Lys Pro Ser  
 290 295 300  
 Ile Glu Phe Glu Asn Ser Phe Gly Asn Leu Ser Phe Gly Thr Leu Leu  
 305 310 315 320  
 Asp Gly Lys Pro Ser Ala Ala Ser Ser Lys Thr Lys Leu Pro Lys Phe  
 325 330 335  
 Thr Ile Leu Gln Thr Ser Glu Val Ser Leu Pro Ser Asp Pro Ser Cys  
 340 345 350  
 Val Glu Glu Ile Leu Arg Glu Ser Gln His Leu Thr Pro Gly Phe Thr  
 355 360 365

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Leu Gln Lys Trp Asn Asp Pro Thr Thr Arg Ala Ser Thr Lys Met Leu  
 370 375 380  
 Glu Asp Asp Leu Lys Leu Ser Ser Asp Glu Asp Asp Leu Glu Pro Val  
 385 390 395 400  
 Lys Thr Leu Thr Thr Gln Cys Thr Ala Thr Glu Leu Tyr Gln Ala Val  
 405 410 415  
 Glu Lys Ala Lys Pro Arg Asn Asn Pro Val Asn Pro Pro Leu Ala Thr  
 420 425 430  
 Pro Gln Pro Pro Pro Ala Val Gln Ala Ser Gly Gly Ser Gly Ser Ser  
 435 440 445  
 Ser Glu Ser Glu Ser Ser Ser Glu Ser Asp Ser Asp Thr Glu Ser Ser  
 450 455 460  
 Thr Thr Asp Ser Glu Ser Asn Glu Ala Pro Arg Val Ala Thr Pro Glu  
 465 470 475 480  
 Pro Glu Pro Pro Ser Thr Asn Lys Trp Gln Leu Asp Lys Trp Leu Asn  
 485 490 495  
 Lys Val Thr Ser Gln Asn Lys Ser Phe Ile Cys Gly Gln Asn Glu Thr  
 500 505 510  
 Pro Met Glu Thr Ile Ser Leu Pro Pro Pro Ile Ile Gln Pro Met Glu  
 515 520 525  
 Val Gln Met Lys Val Lys Thr Asn Ala Ser Gln Val Pro Ala Glu Pro  
 530 535 540  
 Lys Glu Arg Pro Leu Leu Ser Leu Ile Arg Glu Lys Ala Arg Pro Arg  
 545 550 555 560  
 Pro Thr Gln Lys Ile Pro Glu Thr Lys Ala Leu Lys His Lys Leu Ser  
 565 570 575  
 Thr Thr Ser Glu Thr Val Ser Gln Arg Thr Ile Gly Lys Lys Gln Pro  
 580 585 590  
 Lys Lys Val Glu Lys Asn Thr Ser Thr Asp Glu Phe Thr Trp Pro Lys  
 595 600 605  
 Pro Asn Ile Thr Ser Ser Thr Pro Lys Glu Lys Glu Ser Val Glu Leu  
 610 615 620  
 His Asp Pro Pro Arg Gly Arg Asn Lys Ala Thr Ala His Lys Pro Ala  
 625 630 635 640  
 Pro Arg Lys Glu Pro Arg Pro Asn Ile Pro Leu Ala Pro Glu Lys Lys  
 645 650 655  
 Lys Tyr Arg Gly Pro Gly Lys Ile Val Pro Lys Ser Arg Glu Phe Ile  
 660 665 670  
 Glu Thr Asp Ser Ser Thr Ser Asp Ser Asn Thr Asp Gln Glu Glu Thr  
 675 680 685  
 Leu Gln Ile Lys Val Leu Pro Pro Cys Ile Ile Ser Gly Gly Asn Thr  
 690 695 700  
 Ala Lys Ser Lys Glu Ile Cys Gly Ala Ser Leu Thr Leu Ser Thr Leu  
 705 710 715 720  
 Met Ser Ser Ser Gly Ser Asn Asn Asn Leu Ser Ile Ser Asn Glu Glu  
 725 730 735  
 Pro Thr Phe Ser Pro Ile Pro Val Met Gln Thr Glu Ile Leu Ser Pro  
 740 745 750  
 Leu Arg Asp His Glu Asn Leu Lys Asn Leu Trp Val Lys Ile Asp Leu  
 755 760 765  
 Asp Leu Leu Ser Arg Val Pro Gly His Ser Ser Leu His Ala Ala Pro  
 770 775 780  
 Ala Lys Pro Asp His Lys Glu Thr Ala Thr Lys Pro Lys Arg Gln Thr

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|                                                                 |      |      |      |
|-----------------------------------------------------------------|------|------|------|
| 785                                                             | 790  | 795  | 800  |
| Ala Val Thr Ala Val Glu Lys Pro Ala Pro Lys Gly Lys Arg Lys His | 805  | 810  | 815  |
| Lys Pro Ile Glu Val Ala Glu Lys Ile Pro Glu Lys Lys Gln Arg Leu | 820  | 825  | 830  |
| Glu Glu Ala Thr Thr Ile Cys Leu Leu Pro Pro Cys Ile Ser Pro Ala | 835  | 840  | 845  |
| Pro Pro His Lys Pro Pro Asn Thr Arg Glu Asn Asn Ser Ser Arg Arg | 850  | 855  | 860  |
| Ala Asn Arg Arg Lys Glu Glu Lys Leu Phe Pro Pro Pro Leu Ser Pro | 865  | 870  | 875  |
| Leu Pro Glu Asp Pro Pro Arg Arg Arg Asn Val Ser Gly Asn Asn Gly | 885  | 890  | 895  |
| Pro Phe Gly Gln Asp Lys Asn Ile Ala Met Thr Gly Gln Ile Thr Ser | 900  | 905  | 910  |
| Thr Lys Pro Lys Arg Thr Glu Gly Lys Phe Cys Ala Thr Phe Lys Gly | 915  | 920  | 925  |
| Ile Ser Val Asn Glu Gly Asp Thr Pro Lys Lys Ala Ser Ser Ala Thr | 930  | 935  | 940  |
| Ile Thr Val Thr Asn Thr Ala Ile Ala Thr Ala Thr Val Thr Ala Thr | 945  | 950  | 955  |
| Ala Ile Val Thr Thr Val Thr Ala Thr Ala Thr Ala Thr Ala Thr     | 965  | 970  | 975  |
| Thr Thr Thr Thr Thr Thr Thr Ile Ser Thr Ile Thr Ser Thr Ile Thr | 980  | 985  | 990  |
| Thr Gly Leu Met Asp Ser Ser His Leu Glu Met Thr Ser Trp Ala Ala | 995  | 1000 | 1005 |
| Leu Pro Leu Leu Ser Ser Ser Ser Thr Asn Val Arg Arg Pro Lys     | 1010 | 1015 | 1020 |
| Leu Thr Phe Asp Asp Ser Val His Asn Ala Asp Tyr Tyr Met Gln     | 1025 | 1030 | 1035 |
| Glu Ala Lys Lys Leu Lys His Lys Ala Asp Ala Leu Phe Glu Lys     | 1040 | 1045 | 1050 |
| Phe Gly Lys Ala Val Asn Tyr Ala Asp Ala Ala Leu Ser Phe Thr     | 1055 | 1060 | 1065 |
| Glu Cys Gly Asn Ala Met Glu Arg Asp Pro Leu Glu Ala Lys Ser     | 1070 | 1075 | 1080 |
| Pro Tyr Thr Met Tyr Ser Glu Thr Val Glu Leu Leu Arg Tyr Ala     | 1085 | 1090 | 1095 |
| Met Arg Leu Lys Asn Phe Ala Ser Pro Leu Ala Ser Asp Gly Asp     | 1100 | 1105 | 1110 |
| Lys Lys Leu Ala Val Leu Cys Tyr Arg Cys Leu Ser Leu Leu Tyr     | 1115 | 1120 | 1125 |
| Leu Arg Met Phe Lys Leu Lys Lys Asp His Ala Met Lys Tyr Ser     | 1130 | 1135 | 1140 |
| Arg Ser Leu Met Glu Tyr Phe Lys Gln Asn Ala Ser Lys Val Ala     | 1145 | 1150 | 1155 |
| Gln Ile Pro Ser Pro Trp Val Ser Asn Gly Lys Asn Thr Pro Ser     | 1160 | 1165 | 1170 |
| Pro Val Ser Leu Asn Asn Val Ser Pro Ile Asn Ala Met Gly Asn     | 1175 | 1180 | 1185 |
| Cys Asn Asn Gly Pro Val Thr Ile Pro Gln Arg Ile His His Met     | 1190 | 1195 | 1200 |

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|      |     |     |     |     |     |      |     |     |     |     |      |     |     |     |
|------|-----|-----|-----|-----|-----|------|-----|-----|-----|-----|------|-----|-----|-----|
| Ala  | Ala | Ser | His | Val | Asn | Ile  | Thr | Ser | Asn | Val | Leu  | Arg | Gly | Tyr |
| 1205 |     |     |     |     |     | 1210 |     |     |     |     | 1215 |     |     |     |
|      |     |     |     |     |     |      |     |     |     |     |      |     |     |     |
| Glu  | His | Trp | Asp | Met | Ala | Asp  | Lys | Leu | Thr | Arg | Glu  | Asn | Lys | Glu |
| 1220 |     |     |     |     |     | 1225 |     |     |     |     | 1230 |     |     |     |
|      |     |     |     |     |     |      |     |     |     |     |      |     |     |     |
| Phe  | Phe | Gly | Asp | Leu | Asp | Thr  | Leu | Met | Gly | Pro | Leu  | Thr | Gln | His |
| 1235 |     |     |     |     |     | 1240 |     |     |     |     | 1245 |     |     |     |
|      |     |     |     |     |     |      |     |     |     |     |      |     |     |     |
| Ser  | Ser | Met | Thr | Asn | Leu | Val  | Arg | Tyr | Val | Arg | Gln  | Gly | Leu | Cys |
| 1250 |     |     |     |     |     | 1255 |     |     |     |     | 1260 |     |     |     |
|      |     |     |     |     |     |      |     |     |     |     |      |     |     |     |
| Trp  | Leu | Arg | Ile | Asp | Ala | His  | Leu | Leu |     |     |      |     |     |     |
| 1265 |     |     |     |     |     | 1270 |     |     |     |     |      |     |     |     |

&lt;210&gt; SEQ ID NO 38

&lt;211&gt; LENGTH: 2300

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Homo Sapiens

&lt;400&gt; SEQUENCE: 38

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ggccaggcaa gcctgaatcc tgteccctgcc atctcgccac tgcagctcgg gtccagaaag    60
gcaccatttt gtgcggcgtg cccgctctcc cagggggagg agggatcttt ttgcatttt    120
ggagcggcgtg ccaaggaggg gaacctgttg ggcatctccc cagaccgct tgtgagcgcc    180
tccggggcgg gcgggcggga ccagaccct cggggcacgg cgtatcttgg caccggagg    240
cagcggaggc agggcgagca tcctcgctgg gaactggagc tggagtgagc gcaccgcgcg    300
ggaggagccg ccgcagcctc gcagaaccgg agtggaggag gtgacagctc cattgccggg    360
tttttatttt ttttctctcc gcctccccgt ctctctctca ggctcggacc atggtgcagt    420
cccactggct ccctgcccc cctctctgt gagactggct gcggggaggg atcatggata    480
cttgtctgcc ggcttctggt tcccacgcaa gtaagcctgc tgtcaatgga ggaggacatt    540
gatacccgca aaatcaacaa cagtttctctg cgcgaccaca gctatgcgac cgaagctgac    600
attatctcta cggtagaatt caaccacagc ggagaattac tagcgacagg ggacaagggg    660
ggtcggggtg taatatttca acgagagcag gagagtaaaa atcagggtca tcgtaggggt    720
gaatacaatg ttacagcac attccagagc catgaaccgg agttcgatta cctgaagagt    780
ttagaaatag aagaaaaaat caataaaata agatggctcc cccagcagaa tgcagcttac    840
tttctctgt ctactaatga taaaactgtg aagctgtgga aagtcagcga gcgtgataag    900
aggccagaag gctacaatct gaaagatgag gagggccggc tccgggatcc tgccaccatc    960
acaaccctgc ggggtgcctgt cctgagaccc atggacctga tggaggaggc caccaccaga   1020
agagtatttg ccaacgcaca cacatatcac atcaactcca tatctgtcaa cagcgactat   1080
gaaacctaca tgtccgctga tgacctgagg attaacctat ggaactttga aataaccaat   1140
caaagtttta atattgtgga cattaagcca gccaacatgg aggagctcac ggaggatgatc   1200
acagcagccg agttccaccc ccatcattgc aacaccttcg tgtacagcag cagcaaaggg   1260
acaatccggc tgtgtgacat gcgggcatct gccctgtgtg acaggcacac caaatTTTTT   1320
gaagagccgg aagatccaag caacagatca ttttctctg aaattatctc ttcgatttcg   1380
gatgtgaagt tcagccacag tgggaggat atcatgacca gggactactt gaccgtcaaa   1440
gtctgggatc tcaacatgga aaaccgcccc atcgagactt accagggttc tgactacctc   1500
cgcagcaagc tgtgttcctt ctatgaaaat gactgcattt ttgataaatt tgagtgtgtg   1560
tggaatgggt cagacagtgt catcatgaca ggctcctaca acaacttctt caggatgttc   1620
gacagaaaca ccaagcgtga tgtgacctt gaggttcga gggaaaacag caagccccgg   1680
gctatctcta aacccgaaa agtgtgtgtg gggggcaagc ggagaaaaga cgagatcagt   1740

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gtcgacagtc tggacttttag caaaaagatc ttgcatacag cttggcatcc ttcagaaaat 1800
attatagcag tggcggctac aaataaccta tatatatcc aggacaaggt taactagggtg 1860
gacaagttat tacttaataa tctcacatac tgaatactag tcaacaagt ttttaaatgt 1920
ttctttgggt cttcatttga tgcattgact ttaatttccc tatacaggaa atgattggaa 1980
tagaattaaa aggagtccaa cattcccagc tcccagttc taagaaactt ttgtcaaac 2040
caatagggtt gggacacttc tgtttagaat tgaaagctgc cagctaacag taattcttcc 2100
atagttgact tgaacttctg atgcttttat tgcccagttt tctctggtgg gtccagtgtt 2160
ttgttctag gtgtctgctg cgataaaatg aggttgctg tagtatttaa ggagaaaaga 2220
gataagtttt ttttaattaa gcaattccat ttgattgaaa aaaatcaaca aaaataaac 2280
accgtttact cttagacaaa 2300

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&lt;210&gt; SEQ ID NO 39

&lt;211&gt; LENGTH: 443

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Homo Sapiens

&lt;400&gt; SEQUENCE: 39

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Met Glu Glu Asp Ile Asp Thr Arg Lys Ile Asn Asn Ser Phe Leu Arg
1      5      10      15
Asp His Ser Tyr Ala Thr Glu Ala Asp Ile Ile Ser Thr Val Glu Phe
20     25     30
Asn His Thr Gly Glu Leu Leu Ala Thr Gly Asp Lys Gly Gly Arg Val
35     40     45
Val Ile Phe Gln Arg Glu Gln Glu Ser Lys Asn Gln Val His Arg Arg
50     55     60
Gly Glu Tyr Asn Val Tyr Ser Thr Phe Gln Ser His Glu Pro Glu Phe
65     70     75     80
Asp Tyr Leu Lys Ser Leu Glu Ile Glu Glu Lys Ile Asn Lys Ile Arg
85     90     95
Trp Leu Pro Gln Gln Asn Ala Ala Tyr Phe Leu Leu Ser Thr Asn Asp
100    105    110
Lys Thr Val Lys Leu Trp Lys Val Ser Glu Arg Asp Lys Arg Pro Glu
115    120    125
Gly Tyr Asn Leu Lys Asp Glu Glu Gly Arg Leu Arg Asp Pro Ala Thr
130    135    140
Ile Thr Thr Leu Arg Val Pro Val Leu Arg Pro Met Asp Leu Met Val
145    150    155    160
Glu Ala Thr Pro Arg Arg Val Phe Ala Asn Ala His Thr Tyr His Ile
165    170    175
Asn Ser Ile Ser Val Asn Ser Asp Tyr Glu Thr Tyr Met Ser Ala Asp
180    185    190
Asp Leu Arg Ile Asn Leu Trp Asn Phe Glu Ile Thr Asn Gln Ser Phe
195    200    205
Asn Ile Val Asp Ile Lys Pro Ala Asn Met Glu Glu Leu Thr Glu Val
210    215    220
Ile Thr Ala Ala Glu Phe His Pro His His Cys Asn Thr Phe Val Tyr
225    230    235    240
Ser Ser Ser Lys Gly Thr Ile Arg Leu Cys Asp Met Arg Ala Ser Ala
245    250    255
Leu Cys Asp Arg His Thr Lys Phe Phe Glu Glu Pro Glu Asp Pro Ser
260    265    270

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|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asn | Arg | Ser | Phe | Phe | Ser | Glu | Ile | Ile | Ser | Ser | Ile | Ser | Asp | Val | Lys |
|     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |
| Phe | Ser | His | Ser | Gly | Arg | Tyr | Ile | Met | Thr | Arg | Asp | Tyr | Leu | Thr | Val |
|     | 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |
| Lys | Val | Trp | Asp | Leu | Asn | Met | Glu | Asn | Arg | Pro | Ile | Glu | Thr | Tyr | Gln |
| 305 |     |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |
| Val | His | Asp | Tyr | Leu | Arg | Ser | Lys | Leu | Cys | Ser | Leu | Tyr | Glu | Asn | Asp |
|     |     |     |     | 325 |     |     |     |     | 330 |     |     |     |     | 335 |     |
| Cys | Ile | Phe | Asp | Lys | Phe | Glu | Cys | Val | Trp | Asn | Gly | Ser | Asp | Ser | Val |
|     |     |     | 340 |     |     |     |     | 345 |     |     |     |     | 350 |     |     |
| Ile | Met | Thr | Gly | Ser | Tyr | Asn | Asn | Phe | Phe | Arg | Met | Phe | Asp | Arg | Asn |
|     | 355 |     |     |     |     |     | 360 |     |     |     |     | 365 |     |     |     |
| Thr | Lys | Arg | Asp | Val | Thr | Leu | Glu | Ala | Ser | Arg | Glu | Asn | Ser | Lys | Pro |
|     | 370 |     |     |     |     | 375 |     |     |     |     | 380 |     |     |     |     |
| Arg | Ala | Ile | Leu | Lys | Pro | Arg | Lys | Val | Cys | Val | Gly | Gly | Lys | Arg | Arg |
| 385 |     |     |     |     | 390 |     |     |     |     | 395 |     |     |     |     | 400 |
| Lys | Asp | Glu | Ile | Ser | Val | Asp | Ser | Leu | Asp | Phe | Ser | Lys | Lys | Ile | Leu |
|     |     |     |     | 405 |     |     |     |     | 410 |     |     |     |     | 415 |     |
| His | Thr | Ala | Trp | His | Pro | Ser | Glu | Asn | Ile | Ile | Ala | Val | Ala | Ala | Thr |
|     |     |     | 420 |     |     |     |     | 425 |     |     |     |     | 430 |     |     |
| Asn | Asn | Leu | Tyr | Ile | Phe | Gln | Asp | Lys | Val | Asn |     |     |     |     |     |
|     | 435 |     |     |     |     |     | 440 |     |     |     |     |     |     |     |     |

&lt;210&gt; SEQ ID NO 40

&lt;211&gt; LENGTH: 10692

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Homo Sapiens

&lt;400&gt; SEQUENCE: 40

|                                                                    |      |
|--------------------------------------------------------------------|------|
| gaggagagag cagagtatac cgcagacatc atttctacta cagtggcgga gccgtacagg  | 60   |
| acctgtttca ctgcaggggg atccaaaaca agccccgtgg agcagcagcc agagcaacag  | 120  |
| cagccgcaag acattgtttc tctccctctg ccccccttc cccacgcaac cccagatcca   | 180  |
| tttacacttt acagttttac ctcacaaaaa ctactacaag caccaagctc cctgatggaa  | 240  |
| aggagcatcg tgcacaaagt caccagggtg gtccattcaa gctgcagatt tgtttgtcat  | 300  |
| ccttgtacag caatctcttc ctccactgcc actacagga agtgcacac atgtcagcat    | 360  |
| actggagcat agtgaaagag tctattttga agcttcaaac ttagtgctgc tgcagaccag  | 420  |
| gaacaagaga gaaagagtgg atttcagcct gcacggatgg tcttgaaaca caaatggttt  | 480  |
| ttggtctagg cgttttacac tgagattctc cactgccacc ctttctactc aagcaaaatc  | 540  |
| ttcgtgaaaa gatctgctgc aaggaactga tagcttatgg ttctccattg tgatgaaagc  | 600  |
| acatggtaca gttttccaaa gaaattagac cattttcttc gtgagaaaga aatcgacgtg  | 660  |
| ctgttttcat agggatattc tcaacttctc gtgaaaggaa gaaagaacac gcctgagccc  | 720  |
| aagagccctc aggagccctc cagagcctgt ggggaagtct catggtgaag tataggctga  | 780  |
| ggctacctgt gaacagtacg cagtgaatgt tcatccagag ctgctgttgg cggattgtac  | 840  |
| ccacggggag atgattcctc atgaagagcc tggatccctc acagaaatca aatgtgactt  | 900  |
| tccgtttatc agactaaaat cagagccatc cagacagtga aacagtcacc gtggaggggg  | 960  |
| gacggcgaaa aatgaaatcc aaccaagagc ggagcaacga atgcctgcct cccaagaagc  | 1020 |
| gcgagatccc cgccaccagc cggctcctcg aggagaaggc ccctaccctg cccagcgaca  | 1080 |
| accaccgggt ggagggcaca gcatggctcc cgggcaaccc tgggtggccgg ggccacgggg | 1140 |
| gcgggaggca tgggccggca gggacctcgg tggagcttgg tttacaacag ggaataggtt  | 1200 |

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|                                                                    |      |
|--------------------------------------------------------------------|------|
| tacacaaagc attgtccaca gggctggact actccccgcc cagcgctccc aggtctgtcc  | 1260 |
| ccgtggccac cagctgcct gcgcgtacg ccaccccgca gccagggacc ccggtgtccc    | 1320 |
| ccgtgcagta cgtcacctg ccgcacacct tccagttcat tgggtcctcc caatacagt    | 1380 |
| gaacctatgc cagcttcac ccatcacagc tgatccccc aaccgccaac cccgtcacca    | 1440 |
| gtgcagtggc ctcgcccgca ggggccacca ctccatccca gcgtcccag ctggaggcct   | 1500 |
| attccactct gctggccaac atgggcagtc tgagccagac gccgggacac aaggctgagc  | 1560 |
| agcagcagca gcagcagcag cagcagcagc agcagcatca gcatcagcag cagcagcagc  | 1620 |
| agcagcagca gcagcagcag cagcagcacc tcagcagggc tccggggctc atcaccccg   | 1680 |
| ggccccccc accagcccag cagaaccagt acgtccacat ttccagttct ccgcagaaca   | 1740 |
| ccggccgcac cgcctctct ccggccatcc cgtccacct cccccccac cagacgatga     | 1800 |
| ttccacacac gtcaccctg gggccccct cccaggctgt catgcaatac gccgactccg    | 1860 |
| gcagccactt tgtccctcgg gagggccacca agaaagctga gagcagccgg ctgcagcagg | 1920 |
| ccatccaggc caaggaggtc ctgaacgggtg agatggagaa gagccggcgg tacggggccc | 1980 |
| cgtcctcagc cgacctgggc ctgggcaagg caggcggcaa gtcggttcct caccctacg   | 2040 |
| agtcaggca cgtggtggtc caccgagcc cctcagacta cagcagtcgt gatccttcgg    | 2100 |
| gggtccgggc ctctgtgatg gtccctgccca acagcaacac gcccgagct gacctggagg  | 2160 |
| tgcaacaggc cactcatcgt gaagcctccc cttctacct caacgacaaa agtggcctgc   | 2220 |
| atttagggaa gcctggccac cggctctacg cgtctcacc ccacacggtc attcagacca   | 2280 |
| cacacagtgc ttcagagcca ctcccggtg gactgccagc caccgcttc tacgcaggga    | 2340 |
| ctcaaccccc tgtcatcgcc tacctgagcg gccagcagca agcaatcacc tacgccggca  | 2400 |
| gcctgcccc gcacctggg atccccggca cacagccct gctcatccc gtcggcagca      | 2460 |
| ctgacatgga agcgtcggg gcagccccg ccatagtcac gtcatcccc cagtttgctg     | 2520 |
| cagtgcctca cagttcgtc accaccgccc ttcccaagag cgagaacttc aacctgagg    | 2580 |
| ccctggtcac ccaggccgc taccagcca tggtcaggc ccagatccac ctgcctgtgg     | 2640 |
| tgacgtccgt ggctccccg gcggcggctc cccctacgt gcctccctac ttcagtaaag    | 2700 |
| gtccatcat ccagtggcc aacggggagc taaagaagg ggaagactta aaaacagaag     | 2760 |
| atttcatcca gagtgcagag ataagcaacg acctgaagat cgactccagc accgtagaga  | 2820 |
| ggattgaaga cagccatagc ccggcggtg ccgtgataca gttcgccgtc ggggagcacc   | 2880 |
| gagcccaggc cagcgttgaa gttttggtag agtatcctt ttttgtgtt ggacagggct    | 2940 |
| ggteatcctg ctgtccggag agaaccagcc agctctttga tttgccgtgt tccaaactct  | 3000 |
| cagttgggga tgtctgcac tcgcttacct tcaagaacct gaagaacggc tctgttaaaa   | 3060 |
| agggccagcc cgtggatccc gccagcgtc tegtgaagca ctcaaaggcc gacggcctgg   | 3120 |
| cgggcagcag acacaggat gccgagcagg aaaacggaat caaccagggg agtgcccaga   | 3180 |
| tgctctctga gaatggcgaa ctgaagtctc cagagaaaat gggattgcct gcagcgcct   | 3240 |
| tcctaccaa aatagaaccc agcaagccc cggaacgag gaagaggagg tggtcggcgc     | 3300 |
| cagagagccg caaactggag aagtcagaag acgaaccacc tttgactctt cctaagcctt  | 3360 |
| ctctaattcc tcaggagggt aagatttgca ttgaaggccg gtctaagtga ggcaagtaga  | 3420 |
| ggcagcgtg gggaaaggaa acgtggctct cccttatcat ttgtatccag attactgtac   | 3480 |
| tgtaggctaa aataacacag tatttacatg ttatcttctt aattttaggt ttctgttcta  | 3540 |
| accttgtcat tagagttaca gcagggtgt cgcaggagac tggtgcatat gctttttcca   | 3600 |

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|            |             |             |            |            |             |      |
|------------|-------------|-------------|------------|------------|-------------|------|
| cgagtgtctg | tcagtgcgcg  | ggcgggagga  | agggcacagc | aggagcggtc | agggtccag   | 3660 |
| gcatccccgg | ggaagaaagg  | aacggggcctt | cacagtgcct | gccttctcta | gcggcacaga  | 3720 |
| agcagccggg | ggcgtgact   | cccgcctagt  | tcaggagaaa | agtcctgtgg | gaagagtcct  | 3780 |
| gcaggggtgc | agggttgac   | gcattgtggg  | gtgcacaggc | gctgtggcgg | cgagtgcagg  | 3840 |
| tctctttttc | tctgcctccc  | tctgcctcac  | tctcttgcta | tcggcatggg | ccgggggggt  | 3900 |
| tcagagcagt | gtcctcctgg  | ggttcccacg  | tgcaaatca  | acatcaggaa | cccagcttca  | 3960 |
| gggcacgcgg | gagacgcgtc  | agatggcaga  | tttgaaagt  | taaccattta | aaagaacatt  | 4020 |
| ttctctccca | acataattta  | caataaaagc  | aactttta   | tgtatagata | tataattccc  | 4080 |
| cctatggggc | ctgactgcac  | tgatatatat  | tttttttaa  | gagcaactgc | cacatgcggg  | 4140 |
| atttcatttc | tgctttttac  | tagtgcagcg  | atgtcaccag | ggtgttgtgg | tgacagggga  | 4200 |
| agccctgct  | gtcatggccc  | cacatggggt  | aaggggggtt | gggggtgggg | gagagggaga  | 4260 |
| gagcgaacac | ccacgtggt   | ttctgtgcag  | tgtaggaaa  | accaatcagg | ttattgcatt  | 4320 |
| gacttcactc | ccaagaggt   | gatgcaact   | gcccttcagt | gagagcaaca | gaagctcttc  | 4380 |
| acgttgagtt | tgcaaatct   | ttttgtctt   | gaactctagt | actgtttata | gttcattgact | 4440 |
| atggacaact | cgggtgccac  | ttttttttt   | tttcagattc | cagtgtgaca | tgaggaatta  | 4500 |
| gattttgaag | atgagcatat  | attactatct  | ttaagcattt | aaaaatactg | ttcacacttt  | 4560 |
| attaccaagc | atcttggct   | ctcattcaac  | aagtactgta | tctcacttta | aactctttgg  | 4620 |
| ggaaaaaaca | aaaacaaaa   | aaactaagtt  | gctttctttt | tttcaacact | gtaactacat  | 4680 |
| ttcagctctg | cagaattgct  | gaagagcaag  | atattgaaag | tttcaatgtg | gtttaagggg  | 4740 |
| atgaatgtga | attatgaact  | agtatgtgac  | aataaatgac | caccaagtac | tacctgacgg  | 4800 |
| gaggcacttt | tcactttgat  | gtctgagaat  | cagttcaagg | catatgcaga | gttggcagag  | 4860 |
| aaactgagag | aaaagggatg  | gagaagagaa  | tactcatttt | tgtccagtgt | ttttcttttt  | 4920 |
| aagatgaact | tttaagaac   | cttgcgattt  | gcacatattg | agtttataac | ttgtgtgata  | 4980 |
| ttcctgcagt | ttttatccaa  | taacattgtg  | ggaaagggtt | gggggactga | acgagcataa  | 5040 |
| ataaatgtag | caaaatttct  | ttctaacctg  | cctaaactct | aggccatttt | ataaggttat  | 5100 |
| gttcccttga | aaattcattt  | tggtcttttt  | accacatctg | tcacaaaaag | ccaggcttta  | 5160 |
| gcgggctctt | agaaactctg  | agaattttct  | tcagattcat | tgagagagtt | ttccataaag  | 5220 |
| acatttatat | atgtgagcaa  | gatttttttt  | aaacaattac | tttattattg | ttgtatttaa  | 5280 |
| tgttattttc | agaatggcct  | ttttttttct  | attcaaaatc | aaatcgagat | ttaatgtttg  | 5340 |
| gtacaaaacc | agaaagggt   | tttcatagtt  | tttaaacctt | tcattcccag | agatccgaaa  | 5400 |
| tatcatttgt | gggttttgaa  | tgcatcttta  | aagtgcctta | aaaaaaagtt | ttataagtag  | 5460 |
| ggagaaattt | ttaaatatc   | ttacttggat  | ggctgcaact | aaactgaaca | aatacctgac  | 5520 |
| ttttctttta | ccccattgaa  | aatagtactt  | tcttcgtttc | acaaattaaa | aaaaaaatct  | 5580 |
| ggatcaacc  | cacattttgg  | ctgtctagta  | ttcatttaca | tttaggggtc | accaggacta  | 5640 |
| atgattttta | taaacggtt   | tctgggggtg  | accaaaaaca | tttgaatagg | tttagaatag  | 5700 |
| ctagaatagt | tccttgactt  | tcctcgaatt  | tcattaccct | ctcagcatgc | ttgcagagag  | 5760 |
| ctgggtgggc | tcattcttgc  | agtcatactg  | cttatttagt | gctgtatttt | ttaaactgtt  | 5820 |
| ctgttcagag | aacttgcctta | atcttccata  | tattctgctc | agggcacttg | caattattag  | 5880 |
| gttttgtttt | tctttttgtt  | ttttagcctt  | tgatggtaag | aggaatacgg | gctgccacat  | 5940 |
| agacttttgt | ctcattaata  | tcactattta  | caactcatgt | ggactcagaa | aaacacacac  | 6000 |

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| caccttttgg  | cttacttcga  | gtattgaatt | gactggatcc | actaaaccaa  | cactaagatg  | 6060 |
| ggaaaacaca  | catggtttgg  | agcaatagga | acatcatcat | aatttttgtg  | gttctatttc  | 6120 |
| aggtatagga  | attataaaat  | aattggttct | ttctaaacac | ttgtccatt   | tcattctctt  | 6180 |
| gcttttttag  | catgtgcaat  | actttctgtg | ccaatagagt | ctgaccagt   | tgctatatag  | 6240 |
| ttaaagctca  | ttcccttttg  | gctttttcct | tgtttggttg | atcttcccca  | ttctggccag  | 6300 |
| agcagggctg  | gaggggaagg  | gccaggagg  | agagagcctc | ccacctttcc  | cctgctgcgg  | 6360 |
| atgtgagtg   | ctggggcg    | gagccttcag | gagccccgtg | cgtctgccgc  | caggttgca   | 6420 |
| aaagagccag  | ccaagagac   | ccgggggagg | aaccgcagt  | tccctgtca   | ccacacggaa  | 6480 |
| tagtgaatgt  | ggagtgtgga  | gaggaaggag | gcagattcat | ttctaagacg  | cactctggag  | 6540 |
| ccatgtagcc  | tggagtcaac  | ccattttcca | cggcttttcc | tgcaagtggg  | caggcccttc  | 6600 |
| ctcgggggtct | gtgtccttga  | gacttgagc  | cctgcctctg | agcctggacg  | ggaagtgtgg  | 6660 |
| cctgttgtgt  | gtgtgcgttc  | tgagcgtgtt | ggccagtggc | tgtggagggg  | accacctgcc  | 6720 |
| accacggtc   | accactccct  | tgtggcagct | ttctcttcaa | ataggaagaa  | cgcacagagg  | 6780 |
| gcaggagcct  | cctgtttgca  | gacgttgcg  | ggccccgagg | ctcccagagc  | agcctctgtc  | 6840 |
| accgcttctg  | tgtagcaaac  | attaacgatg | acaggggtag | aaattcttcg  | gtgccgttca  | 6900 |
| gcttacaagg  | atcagccatg  | tgccctgtga | ctatgtccac | tttgcaatat  | ttaccgacag  | 6960 |
| ccgtcttttg  | ttctttcttt  | cctgttttcc | atttttaaac | tagtaacagc  | aggccttttg  | 7020 |
| cgtttacaat  | ggaacacaat  | caccaagaaa | ttagtcaggg | cgaagaaaaa  | aaaataatac  | 7080 |
| tattaataag  | aaaccaacaa  | acaagaacct | ctctttctag | ggattttctaa | atatataaaa  | 7140 |
| tgactgttcc  | ttagaatgtt  | taacttaaga | attatttcag | tttgtctggg  | ccacactggg  | 7200 |
| gcagaggggg  | gagggaggga  | tacagagatg | gatgccactt | acctcagatc  | ttttaagtgt  | 7260 |
| gaaatccaaa  | ttgaattttc  | atttggactt | tcaggataat | tttctatgtt  | ggtcaacttt  | 7320 |
| tcgttttccc  | taactcacc   | agtttagttt | gggatgattt | gatttctgtt  | gttgttgatc  | 7380 |
| ccattttctaa | cttggaaatg  | tgagcctcta | tgttttctgt | taggtgagtg  | tgttgggttt  | 7440 |
| ttcccccca   | ccaggaagt   | gcagcatccc | tccttctccc | ctaaagggac  | tctgcggaac  | 7500 |
| ctttcacacc  | tctttctcag  | ggacggggca | gggtgtgtgt | tggtacactg  | acgtgtccag  | 7560 |
| aagcagcact  | ttgactgtc   | tggagttagg | ttgtacaatt | tcaaggaaatg | tttggaattc  | 7620 |
| ctgcactctg  | tggattactc  | cttagatacc | gcatagattg | caatataatg  | ctgcagtgtc  | 7680 |
| aagatgaaca  | gtagctccta  | gtaatcataa | aatccactct | ttgcacagtt  | tgatctttac  | 7740 |
| tgaaatatgt  | tgccaaaatt  | tatttttgtt | gttgtagctc | tggattttgt  | tttgttttgt  | 7800 |
| tttttaagga  | aacgattgac  | aatacccttt | aacatctgtg | actactaagg  | aaacctattt  | 7860 |
| ctttcataga  | gagaaaaatc  | tccaatgctt | ttgaagacac | taataccgtg  | ctatttcaga  | 7920 |
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| aaccctttgc  | acttcaattt  | gcaccaggtg | aaaacagggc | cagcagactc  | catggcccaa  | 8100 |
| ttcggtttct  | tcgggtggtga | tgtgaaagga | gagaattaca | cttttttttt  | ttttaagtgg  | 8160 |
| cgtggaggcc  | tttgcttcca  | catttgtttt | taaccagaa  | tttctgaaat  | agagaattta  | 8220 |
| agaacacatc  | aagtaataaa  | tatacagaga | atatactttt | ttataaagca  | catgcatctg  | 8280 |
| ctattgtgtt  | gggttggttt  | cctctctttt | ccacggacag | tgttgtgttt  | ctggcatagg  | 8340 |
| gaaactccaa  | acaacttgca  | cacctctact | ccggagctga | gatttctttt  | acatagatga  | 8400 |

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|                                                                   |       |
|-------------------------------------------------------------------|-------|
| cctcgcttca aatacgttac cttactgatg ataggatctt ttcttgtagc actatacctt | 8460  |
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| agcactcact ttgaggagta caggtaatgt tttaaaaaat tgcacaaaag aaaaatgaat | 8580  |
| gtcgaaatga ttcattcagt gtttgaaaga tatggctctg ttgaaacaat gagtttcata | 8640  |
| ctttgtttgt aaaaaaaaaa aagcagagaa ggggtgaaag ttacatgttt tttgtatat  | 8700  |
| agaaatttgt catgtctaaa tgatcagatt tgtatggtta tggcctggaa gaattactac | 8760  |
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| gtactctctc gagctccctt cttagtctaa actcttaagc cattgcaact tcttttctt  | 8940  |
| cagagatgat gtttgacatt ttcagcactt cctgttccta taaacccaaa gaatataatc | 9000  |
| ttgaacacga agtgtttgta acaagggatc caggctacca atcaaacagg actcattatg | 9060  |
| gggacaaaaa aaaaaattat ttcaccttct tccccccac acctcattta aatgggggga  | 9120  |
| gtaaaaacat gatttcaatg taaatgcctc attttatttt agttttattt tgatttttat | 9180  |
| ttaataataa gaggccagaa taaatacgga gcatcttctc agaatagtat tccgtgccaa | 9240  |
| aaatcaagcc ggacagtgga aactggacag ctgtggggat attaagcacc cccacttaca | 9300  |
| attcttaaat tcagaatctc gtcccctccc ttctcgttga aggcaactgt tctggtagct | 9360  |
| aactttctcc tgtgtaatgg cgggagggaa caccggcttc agtttttcat gtcccatga  | 9420  |
| cttgcataca aatggttcaa ctgtattaaa attaagtgca tttggccaat aggtagtatc | 9480  |
| tatacaataa caacaatctc taagaatttc cataactttt cttatctgaa aggactcaag | 9540  |
| tcttccactg cagatacatt ggaggcttca cccacgtttt ctttcccttt agtttgtttg | 9600  |
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| gaagtgttgt ttacagtaat ccttaccaag ataacatact gtcctccaga ataccaagta | 9720  |
| ttaggtgaca ctagtccaag ctgttgtctt cagagcagtt accaagaagc tcggtgcaca | 9780  |
| ggttttctct ggttcttaca ggaaccacct actctttcag ttttctggcc caggagtggg | 9840  |
| gtaaatcctt tagttagtgc atttgaactt gatactgtg cattcagttc tgtgaatact  | 9900  |
| gccctttttg gcggggttcc ctcactctcc cagcctgaac tgctcaactc taaacccaaa | 9960  |
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| gagaactagg gaaggaatga tgttttgac cttattgaaa agaaaatttt aagtgcatac  | 10260 |
| ataatagtta agagctttta ttgtgacagg agaacttttt tccatagtgc tgcatactct | 10320 |
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| tggaagaatt catattctat tttctaactg tgggtgtgtc attttagga taaactcgag  | 10440 |
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| aataaattgt ctgtatacca gtacaagttt attgtttcag tatactcgta ctaataaaat | 10620 |
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| aaaaaaaaaa aa                                                     | 10692 |

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<210> SEQ ID NO 41
<211> LENGTH: 798
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 41
Met Lys Ser Asn Gln Glu Arg Ser Asn Glu Cys Leu Pro Pro Lys Lys
1          5          10          15
Arg Glu Ile Pro Ala Thr Ser Arg Ser Ser Glu Glu Lys Ala Pro Thr
          20          25          30
Leu Pro Ser Asp Asn His Arg Val Glu Gly Thr Ala Trp Leu Pro Gly
          35          40          45
Asn Pro Gly Gly Arg Gly His Gly Gly Gly Arg His Gly Pro Ala Gly
          50          55          60
Thr Ser Val Glu Leu Gly Leu Gln Gln Gly Ile Gly Leu His Lys Ala
65          70          75          80
Leu Ser Thr Gly Leu Asp Tyr Ser Pro Pro Ser Ala Pro Arg Ser Val
          85          90          95
Pro Val Ala Thr Thr Leu Pro Ala Ala Tyr Ala Thr Pro Gln Pro Gly
          100          105          110
Thr Pro Val Ser Pro Val Gln Tyr Ala His Leu Pro His Thr Phe Gln
          115          120          125
Phe Ile Gly Ser Ser Gln Tyr Ser Gly Thr Tyr Ala Ser Phe Ile Pro
          130          135          140
Ser Gln Leu Ile Pro Pro Thr Ala Asn Pro Val Thr Ser Ala Val Ala
145          150          155          160
Ser Ala Ala Gly Ala Thr Thr Pro Ser Gln Arg Ser Gln Leu Glu Ala
          165          170          175
Tyr Ser Thr Leu Leu Ala Asn Met Gly Ser Leu Ser Gln Thr Pro Gly
          180          185          190
His Lys Ala Glu Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln
          195          200          205
His Gln His Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln
          210          215          220
Gln His Leu Ser Arg Ala Pro Gly Leu Ile Thr Pro Gly Ser Pro Pro
225          230          235          240
Pro Ala Gln Gln Asn Gln Tyr Val His Ile Ser Ser Ser Pro Gln Asn
          245          250          255
Thr Gly Arg Thr Ala Ser Pro Pro Ala Ile Pro Val His Leu His Pro
          260          265          270
His Gln Thr Met Ile Pro His Thr Leu Thr Leu Gly Pro Pro Ser Gln
          275          280          285
Val Val Met Gln Tyr Ala Asp Ser Gly Ser His Phe Val Pro Arg Glu
          290          295          300
Ala Thr Lys Lys Ala Glu Ser Ser Arg Leu Gln Gln Ala Ile Gln Ala
305          310          315          320
Lys Glu Val Leu Asn Gly Glu Met Glu Lys Ser Arg Arg Tyr Gly Ala
          325          330          335
Pro Ser Ser Ala Asp Leu Gly Leu Gly Lys Ala Gly Gly Lys Ser Val
          340          345          350
Pro His Pro Tyr Glu Ser Arg His Val Val Val His Pro Ser Pro Ser
          355          360          365
Asp Tyr Ser Ser Arg Asp Pro Ser Gly Val Arg Ala Ser Val Met Val
          370          375          380
Leu Pro Asn Ser Asn Thr Pro Ala Ala Asp Leu Glu Val Gln Gln Ala

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|                                                                 |     |     |     |
|-----------------------------------------------------------------|-----|-----|-----|
| 385                                                             | 390 | 395 | 400 |
| Thr His Arg Glu Ala Ser Pro Ser Thr Leu Asn Asp Lys Ser Gly Leu |     |     |     |
|                                                                 | 405 | 410 | 415 |
| His Leu Gly Lys Pro Gly His Arg Ser Tyr Ala Leu Ser Pro His Thr |     |     |     |
|                                                                 | 420 | 425 | 430 |
| Val Ile Gln Thr Thr His Ser Ala Ser Glu Pro Leu Pro Val Gly Leu |     |     |     |
|                                                                 | 435 | 440 | 445 |
| Pro Ala Thr Ala Phe Tyr Ala Gly Thr Gln Pro Pro Val Ile Gly Tyr |     |     |     |
|                                                                 | 450 | 455 | 460 |
| Leu Ser Gly Gln Gln Gln Ala Ile Thr Tyr Ala Gly Ser Leu Pro Gln |     |     |     |
|                                                                 | 465 | 470 | 480 |
| His Leu Val Ile Pro Gly Thr Gln Pro Leu Leu Ile Pro Val Gly Ser |     |     |     |
|                                                                 | 485 | 490 | 495 |
| Thr Asp Met Glu Ala Ser Gly Ala Ala Pro Ala Ile Val Thr Ser Ser |     |     |     |
|                                                                 | 500 | 505 | 510 |
| Pro Gln Phe Ala Ala Val Pro His Thr Phe Val Thr Thr Ala Leu Pro |     |     |     |
|                                                                 | 515 | 520 | 525 |
| Lys Ser Glu Asn Phe Asn Pro Glu Ala Leu Val Thr Gln Ala Ala Tyr |     |     |     |
|                                                                 | 530 | 535 | 540 |
| Pro Ala Met Val Gln Ala Gln Ile His Leu Pro Val Val Gln Ser Val |     |     |     |
|                                                                 | 545 | 550 | 555 |
| Ala Ser Pro Ala Ala Ala Pro Pro Thr Leu Pro Pro Tyr Phe Met Lys |     |     |     |
|                                                                 | 565 | 570 | 575 |
| Gly Ser Ile Ile Gln Leu Ala Asn Gly Glu Leu Lys Lys Val Glu Asp |     |     |     |
|                                                                 | 580 | 585 | 590 |
| Leu Lys Thr Glu Asp Phe Ile Gln Ser Ala Glu Ile Ser Asn Asp Leu |     |     |     |
|                                                                 | 595 | 600 | 605 |
| Lys Ile Asp Ser Ser Thr Val Glu Arg Ile Glu Asp Ser His Ser Pro |     |     |     |
|                                                                 | 610 | 615 | 620 |
| Gly Val Ala Val Ile Gln Phe Ala Val Gly Glu His Arg Ala Gln Val |     |     |     |
|                                                                 | 625 | 630 | 635 |
| Ser Val Glu Val Leu Val Glu Tyr Pro Phe Phe Val Phe Gly Gln Gly |     |     |     |
|                                                                 | 645 | 650 | 655 |
| Trp Ser Ser Cys Cys Pro Glu Arg Thr Ser Gln Leu Phe Asp Leu Pro |     |     |     |
|                                                                 | 660 | 665 | 670 |
| Cys Ser Lys Leu Ser Val Gly Asp Val Cys Ile Ser Leu Thr Leu Lys |     |     |     |
|                                                                 | 675 | 680 | 685 |
| Asn Leu Lys Asn Gly Ser Val Lys Lys Gly Gln Pro Val Asp Pro Ala |     |     |     |
|                                                                 | 690 | 695 | 700 |
| Ser Val Leu Leu Lys His Ser Lys Ala Asp Gly Leu Ala Gly Ser Arg |     |     |     |
|                                                                 | 705 | 710 | 715 |
| His Arg Tyr Ala Glu Gln Glu Asn Gly Ile Asn Gln Gly Ser Ala Gln |     |     |     |
|                                                                 | 725 | 730 | 735 |
| Met Leu Ser Glu Asn Gly Glu Leu Lys Phe Pro Glu Lys Met Gly Leu |     |     |     |
|                                                                 | 740 | 745 | 750 |
| Pro Ala Ala Pro Phe Leu Thr Lys Ile Glu Pro Ser Lys Pro Ala Ala |     |     |     |
|                                                                 | 755 | 760 | 765 |
| Thr Arg Lys Arg Arg Trp Ser Ala Pro Glu Ser Arg Lys Leu Glu Lys |     |     |     |
|                                                                 | 770 | 775 | 780 |
| Ser Glu Asp Glu Pro Pro Leu Thr Leu Pro Lys Pro Ser Leu         |     |     |     |
|                                                                 | 785 | 790 | 795 |

&lt;210&gt; SEQ ID NO 42

&lt;211&gt; LENGTH: 4702

-continued

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Homo Sapiens

&lt;400&gt; SEQUENCE: 42

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cacctccgct cccaccggcg gcctcggcgc gcccgccctc cgatgcgctc agcggccgca    180
gctcctcgga gtcccgcggg ggccaccgag tctcgccgct tcgccgcagc caggtggccc    240
gggtggcgct cgctccagcg gccggcgcgg cggagcgggc ggggcggcgg tggcgcggcc    300
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aggatggttc atatacttac atcagttggt ggctccaaat gtgaagtaca agtgaaaaat   1020
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agtattttgt tcaaatgttc agactttggt gtggtacagt ttaagatat ggactccagt   1200
tatgcaaaaa gagatgcttt tactgactct gctatcagtg ctaaaagtga tggcgaaacac   1260
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ctagaatttg tatccccaaa cccaccagtg gaagcagcta ctctccagt agcaaggacc   2160
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|-------------|------------|-------------|-------------|-------------|-------------|------|
| cttgccttctc | cccaagctgg | tattattcca  | actgaagctg  | ttgccatgcc  | tattccagct  | 2340 |
| gcattctccta | cgctgctag  | tcctgcatcg  | aacagagctg  | ttaccoccttc | tagtgaggct  | 2400 |
| aaagattcca  | ggcttcaaga | tcagaggcag  | aactctctctg | caggaataa   | agaaaatatt  | 2460 |
| aaaccaatg   | aaacatcacc | tagcttctca  | aaagctgaaa  | acaaggtat   | atcaccagtt  | 2520 |
| gtttctgaac  | atagaaaaca | gattgatgat  | ttaaagaaat  | ttaagaatga  | ttttaggtta  | 2580 |
| cagccaagtt  | ctacttctga | atctatggat  | caactactaa  | acaaaaatag  | agagggagaa  | 2640 |
| aatcaagag   | atttgatcaa | agacaaaatt  | gaaccaagtg  | ctaaggattc  | tttcattgaa  | 2700 |
| aatagcagca  | gcaactgtac | cagtggcagc  | agcaagccga  | atagccccag  | catttcccct  | 2760 |
| tcaatactta  | gtaacacgga | gcacaagagg  | ggacctgagg  | tcacttccca  | aggggttcag  | 2820 |
| acttccagcc  | cagcatgtaa | acaagagaaa  | gacgataagg  | aagagaagaa  | agacgcagct  | 2880 |
| gagcaagtta  | ggaaatcaac | attgaatccc  | aatgcaaagg  | agttcaaccc  | acgttccttc  | 2940 |
| tctcagccaa  | agccttctac | taccccaact  | tcacctcggc  | ctcaagcaca  | acctagccca  | 3000 |
| tctatggtgg  | gtcatcaaca | gccaaactcca | gtttatactc  | agcctgtttg  | ttttgcacca  | 3060 |
| aatatgatgt  | atccagtccc | agtgagccca  | ggcgtgcaac  | ctttataccc  | aatacctatg  | 3120 |
| acgcccatgc  | cagtgaatca | agccaagaca  | tatagagcag  | taccaaata   | gccccaacag  | 3180 |
| cggaagacc   | agcatcatca | gagtgccatg  | atgcacccag  | cgtcagcagc  | gggccaccg   | 3240 |
| attgcagcca  | ccccaccagc | ttactccacg  | caatatgttg  | cctacagtcc  | tcagcagttc  | 3300 |
| ccaaatcagc  | cccttgttca | gcattgtgcca | cattatcagt  | ctcagcatcc  | tcattgtctat | 3360 |
| agtctgttaa  | tacagggtaa | tgctagaatg  | atggcaccac  | caacacacgc  | ccagcctggt  | 3420 |
| ttagtatcct  | cttcagcaac | tcagtacggg  | gctcatgagc  | agacgcattg  | gatgtatgca  | 3480 |
| tgccccaaat  | taccatacaa | caaggagaca  | agcccttctt  | tctactttgc  | catttccacg  | 3540 |
| ggctcccttg  | ctcagcagta | tgcgacccct  | aacgctaccc  | tgcacccaca  | tactccacac  | 3600 |
| cctcagcctt  | cagctacccc | cactggacag  | cagcaaagcc  | aacatggttg  | aagtcacct   | 3660 |
| gcaccagtc   | ctgttcagca | ccatcagcac  | caggccgccc  | aggetctcca  | tctggccagt  | 3720 |
| ccacagcagc  | agtcagccat | ttaccacgcg  | gggcttgccg  | caactccacc  | ctccatgaca  | 3780 |
| cctgcctcca  | acacgcagtc | gccacagaat  | agtttcccag  | cagcacaaca  | gactgtcttt  | 3840 |
| acgatccatc  | cttctcacgt | tcagccggcg  | tataccaacc  | caccccacat  | ggcccacgta  | 3900 |
| cctcaggctc  | atgtacagtc | aggaatggtt  | ccttctcatc  | caactgcccc  | tgcgccaatg  | 3960 |
| atgctaata   | cgacacagcc | acccggcggt  | ccccaggccg  | ccctcgctca  | aagtgcacta  | 4020 |
| cagcccattc  | cagtctcgac | aacagcgcac  | ttcccctata  | tgaagcagcc  | ttcagtacaa  | 4080 |
| gcccaccacc  | aacagcagtt | gtaaggctgc  | cctggaggaa  | cgaagaggcc  | aaattccctc  | 4140 |
| ctcccttcta  | ctgcttctac | caactggaag  | cacagaaaac  | tagaatttca  | tttattttgt  | 4200 |
| ttttaaaata  | tatatgttga | tttcttgtaa  | catccaatag  | gaatgctaac  | agttcacttg  | 4260 |
| cagtgaaga   | tacttgagcc | gagtagaggc  | atttaggaac  | ttgggggcta  | ttccataatt  | 4320 |
| ccatatgctg  | tttcagagtc | ccgcaggtag  | cccagctctg  | cttgccgaaa  | ctggaagtta  | 4380 |
| tttatttttt  | aataaccctt | gaaagtcatg  | aacacatcag  | ctagcaaaaag | aagtaacaag  | 4440 |
| agtgattctt  | gtgctatta  | ctgctaaaaa  | aaaaaaaaaa  | aaaaaatcaa  | gacttggaac  | 4500 |
| gcccctttac  | taaacttgac | aaagtttcag  | taaattctta  | ccgtcaaaact | gacggattat  | 4560 |
| tatttataaa  | tcaagtttga | tgaggtgatc  | actgtctaca  | gtggttcaac  | ttttaagtta  | 4620 |
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4702

&lt;210&gt; SEQ ID NO 43

&lt;211&gt; LENGTH: 1313

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Homo Sapiens

&lt;400&gt; SEQUENCE: 43

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 Arg Pro Ala Arg Arg Ser Gly Arg Gly Gly Gly Ala Ala Pro Gly  
 35 40 45  
 Pro Tyr Pro Ser Ala Ala Pro Pro Pro Gly Pro Gly Pro Pro Pro  
 50 55 60  
 Ser Arg Gln Ser Ser Pro Pro Ser Ala Ser Asp Cys Phe Gly Ser Asn  
 65 70 75 80  
 Gly Asn Gly Gly Gly Ala Phe Arg Pro Gly Ser Arg Arg Leu Leu Gly  
 85 90 95  
 Leu Gly Gly Pro Pro Arg Pro Phe Val Val Val Leu Leu Pro Leu Ala  
 100 105 110  
 Ser Pro Gly Ala Pro Pro Ala Ala Pro Thr Arg Ala Ser Pro Leu Gly  
 115 120 125  
 Ala Arg Ala Ser Pro Pro Arg Ser Gly Val Ser Leu Ala Arg Pro Ala  
 130 135 140  
 Pro Gly Cys Pro Arg Pro Ala Cys Glu Pro Val Tyr Gly Pro Leu Thr  
 145 150 155 160  
 Met Ser Leu Lys Pro Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln  
 165 170 175  
 Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Pro Pro Pro Ala  
 180 185 190  
 Ala Ala Asn Val Arg Lys Pro Gly Gly Ser Gly Leu Leu Ala Ser Pro  
 195 200 205  
 Ala Ala Ala Pro Ser Pro Ser Ser Ser Val Ser Ser Ser Ser Ala  
 210 215 220  
 Thr Ala Pro Ser Ser Val Val Ala Ala Thr Ser Gly Gly Gly Arg Pro  
 225 230 235 240  
 Gly Leu Gly Arg Gly Arg Asn Ser Asn Lys Gly Leu Pro Gln Ser Thr  
 245 250 255  
 Ile Ser Phe Asp Gly Ile Tyr Ala Asn Met Arg Met Val His Ile Leu  
 260 265 270  
 Thr Ser Val Val Gly Ser Lys Cys Glu Val Gln Val Lys Asn Gly Gly  
 275 280 285  
 Ile Tyr Glu Gly Val Phe Lys Thr Tyr Ser Pro Lys Cys Asp Leu Val  
 290 295 300  
 Leu Asp Ala Ala His Glu Lys Ser Thr Glu Ser Ser Ser Gly Pro Lys  
 305 310 315 320  
 Arg Glu Glu Ile Met Glu Ser Ile Leu Phe Lys Cys Ser Asp Phe Val  
 325 330 335  
 Val Val Gln Phe Lys Asp Met Asp Ser Ser Tyr Ala Lys Arg Asp Ala  
 340 345 350  
 Phe Thr Asp Ser Ala Ile Ser Ala Lys Val Asn Gly Glu His Lys Glu  
 355 360 365

|            |     |            |            |            |            |            |            |            |            |            |            |            |            |            |            |
|------------|-----|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| Lys<br>370 | Asp | Leu        | Glu        | Pro        | Trp        | Asp<br>375 | Ala        | Gly        | Glu        | Leu        | Thr<br>380 | Ala        | Asn        | Glu        | Glu        |
| Leu<br>385 | Glu | Ala        | Leu        | Glu        | Asn<br>390 | Asp        | Val        | Ser        | Asn        | Gly<br>395 | Trp        | Asp        | Pro        | Asn        | Asp<br>400 |
| Met        | Phe | Arg        | Tyr        | Asn<br>405 | Glu        | Glu        | Asn        | Tyr        | Gly<br>410 | Val        | Val        | Ser        | Thr        | Tyr        | Asp<br>415 |
| Ser        | Ser | Leu        | Ser        | Ser        | Tyr        | Thr        | Val        | Pro<br>425 | Leu        | Glu        | Arg        | Asp        | Asn<br>430 | Ser        | Glu        |
| Glu        | Phe | Leu        | Lys        | Arg        | Glu        | Ala        | Arg<br>440 | Ala        | Asn        | Gln        | Leu        | Ala<br>445 | Glu        | Glu        | Ile        |
| Glu        | Ser | Ser        | Ala        | Gln        | Tyr        | Lys<br>455 | Ala        | Arg        | Val        | Ala        | Leu        | Glu        | Asn        | Asp        | Asp        |
| Arg<br>465 | Ser | Glu        | Glu        | Glu        | Lys<br>470 | Tyr        | Thr        | Ala        | Val        | Gln        | Arg        | Asn        | Ser        | Ser        | Glu<br>480 |
| Arg        | Glu | Gly        | His        | Ser<br>485 | Ile        | Asn        | Thr        | Arg        | Glu<br>490 | Asn        | Lys        | Tyr        | Ile        | Pro<br>495 | Pro        |
| Gly        | Gln | Arg        | Asn<br>500 | Arg        | Glu        | Val        | Ile        | Ser<br>505 | Trp        | Gly        | Ser        | Gly        | Arg<br>510 | Gln        | Asn        |
| Ser        | Pro | Arg<br>515 | Met        | Gly        | Gln        | Pro        | Gly<br>520 | Ser        | Gly        | Ser        | Met        | Pro<br>525 | Ser        | Arg        | Ser        |
| Thr<br>530 | Ser | His        | Thr        | Ser        | Asp<br>535 | Phe        | Asn        | Pro        | Asn        | Ser        | Gly<br>540 | Ser        | Asp        | Gln        | Arg        |
| Val<br>545 | Val | Asn        | Gly        | Gly        | Val<br>550 | Pro        | Trp        | Pro        | Ser        | Pro<br>555 | Cys        | Pro        | Ser        | Pro        | Ser<br>560 |
| Ser        | Arg | Pro        | Pro        | Ser<br>565 | Arg        | Tyr        | Gln        | Ser        | Gly<br>570 | Pro        | Asn        | Ser        | Leu        | Pro<br>575 | Pro        |
| Arg        | Ala | Ala        | Thr<br>580 | Pro        | Thr        | Arg        | Pro        | Pro<br>585 | Ser        | Arg        | Pro        | Pro        | Ser<br>590 | Arg        | Pro        |
| Ser        | Arg | Pro<br>595 | Pro        | Ser        | His        | Pro        | Ser<br>600 | Ala        | His        | Gly        | Ser        | Pro<br>605 | Ala        | Pro        | Val        |
| Ser<br>610 | Thr | Met        | Pro        | Lys        | Arg        | Met<br>615 | Ser        | Ser        | Glu        | Gly        | Pro<br>620 | Pro        | Arg        | Met        | Ser        |
| Pro<br>625 | Lys | Ala        | Gln        | Arg        | His<br>630 | Pro        | Arg        | Asn        | His        | Arg<br>635 | Val        | Ser        | Ala        | Gly        | Arg<br>640 |
| Gly        | Ser | Ile        | Ser<br>645 | Ser        | Gly        | Leu        | Glu        | Phe        | Val<br>650 | Ser        | His        | Asn        | Pro        | Pro        | Ser<br>655 |
| Glu        | Ala | Ala        | Thr<br>660 | Pro        | Pro        | Val        | Ala        | Arg<br>665 | Thr        | Ser        | Pro        | Ser        | Gly<br>670 | Gly        | Thr        |
| Trp        | Ser | Ser<br>675 | Val        | Val        | Ser        | Gly        | Val<br>680 | Pro        | Arg        | Leu        | Ser        | Pro<br>685 | Lys        | Thr        | His        |
| Arg<br>690 | Pro | Arg        | Ser        | Pro        | Arg        | Gln<br>695 | Asn        | Ser        | Ile        | Gly        | Asn<br>700 | Thr        | Pro        | Ser        | Gly        |
| Pro<br>705 | Val | Leu        | Ala        | Ser        | Pro        | Gln        | Ala        | Gly        | Ile<br>715 | Ile        | Pro        | Thr        | Glu        | Ala        | Val<br>720 |
| Ala        | Met | Pro        | Ile<br>725 | Pro        | Ala        | Ala        | Ser        | Pro        | Thr<br>730 | Pro        | Ala        | Ser        | Pro        | Ala        | Ser<br>735 |
| Asn        | Arg | Ala<br>740 | Val        | Thr        | Pro        | Ser        | Ser        | Glu<br>745 | Ala        | Lys        | Asp        | Ser        | Arg<br>750 | Leu        | Gln        |
| Asp        | Gln | Arg<br>755 | Gln        | Asn        | Ser        | Pro        | Ala<br>760 | Gly        | Asn        | Lys        | Glu        | Asn<br>765 | Ile        | Lys        | Pro        |
| Asn<br>770 | Glu | Thr        | Ser        | Pro        | Ser        | Phe<br>775 | Ser        | Lys        | Ala        | Glu        | Asn<br>780 | Lys        | Gly        | Ile        | Ser        |
| Pro<br>785 | Val | Val        | Ser        | Glu        | His<br>790 | Arg        | Lys        | Gln        | Ile<br>795 | Asp        | Asp        | Leu        | Lys        | Lys        | Phe<br>800 |

|     |     |     |      |     |     |     |     |     |      |     |     |      |     |     |     |
|-----|-----|-----|------|-----|-----|-----|-----|-----|------|-----|-----|------|-----|-----|-----|
| Lys | Asn | Asp | Phe  | Arg | Leu | Gln | Pro | Ser | Ser  | Thr | Ser | Glu  | Ser | Met | Asp |
|     |     |     | 805  |     |     |     |     |     | 810  |     |     | 815  |     |     |     |
| Gln | Leu | Leu | Asn  | Lys | Asn | Arg | Glu | Gly | Glu  | Lys | Ser | Arg  | Asp | Leu | Ile |
|     |     |     | 820  |     |     |     |     |     | 825  |     |     | 830  |     |     |     |
| Lys | Asp | Lys | Ile  | Glu | Pro | Ser | Ala | Lys | Asp  | Ser | Phe | Ile  | Glu | Asn | Ser |
|     |     |     | 835  |     |     |     |     |     | 840  |     |     | 845  |     |     |     |
| Ser | Ser | Asn | Cys  | Thr | Ser | Gly | Ser | Ser | Lys  | Pro | Asn | Ser  | Pro | Ser | Ile |
|     |     |     | 850  |     |     |     |     |     | 855  |     |     | 860  |     |     |     |
| Ser | Pro | Ser | Ile  | Leu | Ser | Asn | Thr | Glu | His  | Lys | Arg | Gly  | Pro | Glu | Val |
|     |     |     | 865  |     |     |     |     |     | 870  |     |     | 875  |     |     |     |
| Thr | Ser | Gln | Gly  | Val | Gln | Thr | Ser | Ser | Pro  | Ala | Cys | Lys  | Gln | Glu | Lys |
|     |     |     | 885  |     |     |     |     |     | 890  |     |     | 895  |     |     |     |
| Asp | Asp | Lys | Glu  | Glu | Lys | Lys | Asp | Ala | Ala  | Glu | Gln | Val  | Arg | Lys | Ser |
|     |     |     | 900  |     |     |     |     |     | 905  |     |     | 910  |     |     |     |
| Thr | Leu | Asn | Pro  | Asn | Ala | Lys | Glu | Phe | Asn  | Pro | Arg | Ser  | Phe | Ser | Gln |
|     |     |     | 915  |     |     |     |     |     | 920  |     |     | 925  |     |     |     |
| Pro | Lys | Pro | Ser  | Thr | Thr | Pro | Thr | Ser | Pro  | Arg | Pro | Gln  | Ala | Gln | Pro |
|     |     |     | 930  |     |     |     |     |     | 935  |     |     | 940  |     |     |     |
| Ser | Pro | Ser | Met  | Val | Gly | His | Gln | Gln | Pro  | Thr | Pro | Val  | Tyr | Thr | Gln |
|     |     |     | 945  |     |     |     |     |     | 950  |     |     | 955  |     |     |     |
| Pro | Val | Cys | Phe  | Ala | Pro | Asn | Met | Met | Tyr  | Pro | Val | Pro  | Val | Ser | Pro |
|     |     |     | 965  |     |     |     |     |     | 970  |     |     | 975  |     |     |     |
| Gly | Val | Gln | Pro  | Leu | Tyr | Pro | Ile | Pro | Met  | Thr | Pro | Met  | Pro | Val | Asn |
|     |     |     | 980  |     |     |     |     |     | 985  |     |     | 990  |     |     |     |
| Gln | Ala | Lys | Thr  | Tyr | Arg | Ala | Val | Pro | Asn  | Met | Pro | Gln  | Gln | Arg | Gln |
|     |     |     | 995  |     |     |     |     |     | 1000 |     |     | 1005 |     |     |     |
| Asp | Gln | His | His  | Gln | Ser | Ala | Met | Met | His  | Pro | Ala | Ser  | Ala | Ala |     |
|     |     |     | 1010 |     |     |     |     |     | 1015 |     |     | 1020 |     |     |     |
| Gly | Pro | Pro | Ile  | Ala | Ala | Thr | Pro | Pro | Ala  | Tyr | Ser | Thr  | Gln | Tyr |     |
|     |     |     | 1025 |     |     |     |     |     | 1030 |     |     | 1035 |     |     |     |
| Val | Ala | Tyr | Ser  | Pro | Gln | Gln | Phe | Pro | Asn  | Gln | Pro | Leu  | Val | Gln |     |
|     |     |     | 1040 |     |     |     |     |     | 1045 |     |     | 1050 |     |     |     |
| His | Val | Pro | His  | Tyr | Gln | Ser | Gln | His | Pro  | His | Val | Tyr  | Ser | Pro |     |
|     |     |     | 1055 |     |     |     |     |     | 1060 |     |     | 1065 |     |     |     |
| Val | Ile | Gln | Gly  | Asn | Ala | Arg | Met | Met | Ala  | Pro | Pro | Thr  | His | Ala |     |
|     |     |     | 1070 |     |     |     |     |     | 1075 |     |     | 1080 |     |     |     |
| Gln | Pro | Gly | Leu  | Val | Ser | Ser | Ser | Ala | Thr  | Gln | Tyr | Gly  | Ala | His |     |
|     |     |     | 1085 |     |     |     |     |     | 1090 |     |     | 1095 |     |     |     |
| Glu | Gln | Thr | His  | Ala | Met | Tyr | Ala | Cys | Pro  | Lys | Leu | Pro  | Tyr | Asn |     |
|     |     |     | 1100 |     |     |     |     |     | 1105 |     |     | 1110 |     |     |     |
| Lys | Glu | Thr | Ser  | Pro | Ser | Phe | Tyr | Phe | Ala  | Ile | Ser | Thr  | Gly | Ser |     |
|     |     |     | 1115 |     |     |     |     |     | 1120 |     |     | 1125 |     |     |     |
| Leu | Ala | Gln | Gln  | Tyr | Ala | His | Pro | Asn | Ala  | Thr | Leu | His  | Pro | His |     |
|     |     |     | 1130 |     |     |     |     |     | 1135 |     |     | 1140 |     |     |     |
| Thr | Pro | His | Pro  | Gln | Pro | Ser | Ala | Thr | Pro  | Thr | Gly | Gln  | Gln | Gln |     |
|     |     |     | 1145 |     |     |     |     |     | 1150 |     |     | 1155 |     |     |     |
| Ser | Gln | His | Gly  | Gly | Ser | His | Pro | Ala | Pro  | Ser | Pro | Val  | Gln | His |     |
|     |     |     | 1160 |     |     |     |     |     | 1165 |     |     | 1170 |     |     |     |
| His | Gln | His | Gln  | Ala | Ala | Gln | Ala | Leu | His  | Leu | Ala | Ser  | Pro | Gln |     |
|     |     |     | 1175 |     |     |     |     |     | 1180 |     |     | 1185 |     |     |     |
| Gln | Gln | Ser | Ala  | Ile | Tyr | His | Ala | Gly | Leu  | Ala | Pro | Thr  | Pro | Pro |     |
|     |     |     | 1190 |     |     |     |     |     | 1195 |     |     | 1200 |     |     |     |
| Ser | Met | Thr | Pro  | Ala | Ser | Asn | Thr | Gln | Ser  | Pro | Gln |      |     |     |     |

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| 1205                                                               | 1210 | 1215 |  |
|--------------------------------------------------------------------|------|------|--|
| Pro Ala Ala Gln Gln Thr Val Phe Thr Ile His Pro Ser His Val        |      |      |  |
| 1220                                                               | 1225 | 1230 |  |
| Gln Pro Ala Tyr Thr Asn Pro Pro His Met Ala His Val Pro Gln        |      |      |  |
| 1235                                                               | 1240 | 1245 |  |
| Ala His Val Gln Ser Gly Met Val Pro Ser His Pro Thr Ala His        |      |      |  |
| 1250                                                               | 1255 | 1260 |  |
| Ala Pro Met Met Leu Met Thr Thr Gln Pro Pro Gly Gly Pro Gln        |      |      |  |
| 1265                                                               | 1270 | 1275 |  |
| Ala Ala Leu Ala Gln Ser Ala Leu Gln Pro Ile Pro Val Ser Thr        |      |      |  |
| 1280                                                               | 1285 | 1290 |  |
| Thr Ala His Phe Pro Tyr Met Thr His Pro Ser Val Gln Ala His        |      |      |  |
| 1295                                                               | 1300 | 1305 |  |
| His Gln Gln Gln Leu                                                |      |      |  |
| 1310                                                               |      |      |  |
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| <211> LENGTH: 2678                                                 |      |      |  |
| <212> TYPE: DNA                                                    |      |      |  |
| <213> ORGANISM: Homo Sapiens                                       |      |      |  |
| <400> SEQUENCE: 44                                                 |      |      |  |
| ggggcggagc tggagggggt gggtcggcgt gggggccgtt ggctccagac aaataaacat  | 60   |      |  |
| ggagtccatc ttccacgaga aacaagaagg ctactttgt gctcaacatt gcctgaataa   | 120  |      |  |
| cttattgcaa ggagaatatt ttagccctgt ggaattatcc tcaattgcac atcagctgga  | 180  |      |  |
| tgaggaggag aggatgagaa tggcagaagg aggagttact agtgaagatt atcgacggt   | 240  |      |  |
| tttacagcag ccttctggaa atatggatga cagtgggttt ttctctattc aggttataag  | 300  |      |  |
| caatgccttg aaagtttggg gtttagaact aatcctgttc aacagtccag agtatcagag  | 360  |      |  |
| gctcaggatc gatcctataa atgaaagatc atttatatgc aattataagg aacactggtt  | 420  |      |  |
| tacagttaga aaattaggaa aacagtgtt taacttgaat tctctcttga cgggtccaga   | 480  |      |  |
| attaatatca gatacatatc ttgcactttt cttggctcaa ttacaacagg aaggttattc  | 540  |      |  |
| tatatattgtc gttaagggtg atctgccaga ttgcgaagct gaccaactcc tgcagatgat | 600  |      |  |
| taggggccaa catagtcacg gacccaaact tattggagaa gaattagcac aactaaaaga  | 660  |      |  |
| gcaaagagtc cataaaacag acctggaacg agtggttagaa gcaaatgatg gctcaggaat | 720  |      |  |
| gttagacgaa gatgaggagg atttgcagag ggctctggca ctaagtcgcc aagaaattga  | 780  |      |  |
| catggaagat gaggaagcag atctccgcag ggctattcag ctaagtatgc aaggtagttc  | 840  |      |  |
| cagaaacata tctcaagata tgacacagac atcaggtaca aatcttactt cagaagagct  | 900  |      |  |
| tcggaagaga cgagaagcct actttgaaaa acagcagcaa aagcagcaac agcagcagca  | 960  |      |  |
| gcagcagcag caggggggacc tatcaggaca gagttcacat ccatgtgaaa ggccagccac | 1020 |      |  |
| cagttcagga gcacttggga gtgatctagg tgatgctatg agtgaagaag acatgcttca  | 1080 |      |  |
| ggcagctgtg accatgtctt tagaaactgt cagaaatgat ttgaaaacag aaggaaaaaa  | 1140 |      |  |
| ataatacctt taaaaataa tttagatatt catactttcc aacattatcc tgtgtgatta   | 1200 |      |  |
| cagcataggg tccacttttg taatgtgtca aagagatgag gaaataagac ttttagcggg  | 1260 |      |  |
| ttgcaaacaa aatgatggga aagtgaaca atgcgtcggg ttaggacta aataatgatc    | 1320 |      |  |
| ttccaaatat tagccaaaga ggcattcagc aattaaagac atttaaaata gttttctaaa  | 1380 |      |  |
| tgtttctttt tcttttttga gtgtgcaata tgtaacatgt ctaaagttag ggcatttttc  | 1440 |      |  |
| ttggatcttt ttgcagacta gctaattagc tctcgcctca ggctttttcc atatagtttg  | 1500 |      |  |

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ttttcttttt ctgtcttgta ggtaagttgg ctcacatcat gtaatagtgg ctttcatttc 1560
ttattaacca aattaacctt tcaggaaagt atctctactt tcctgatggt gataatagta 1620
atgggtctag aaggatgaac agttctccct tcaactgtat accgtgtgct ccagtgtttt 1680
cttggtgtgt tttctctgat cacaactttt ctgctacctg gttttcatta tttcccaca 1740
attcttttga aagatggtaa tcttttctga ggttttagcgt ttttaagccct acgatgggat 1800
cattatttca tgactgggtgc gttcctaaac tctgaaatca gccttgacaca agtacttgag 1860
aataaatgag ctttttttaa aatgtgtgag catgtgcttt ccagatgct ttatgaatgt 1920
cttttcactt atatcaaaac cttacagctt tgttgcaacc ccttcttctt gcgccttatt 1980
ttttcctttc ttctccaatt gagaaaacta ggagaagcat agtatgcagg caagtctcct 2040
tctgttagaa gactaaacat acgtaccac catgaatgta tgatacatga aatttggcct 2100
tcaattttaa tagcagtttt attttatttt ttctcctatg actggagctt tgtgttctct 2160
ttacagttga gtcattggaat gtaggtgtct gcttcacatc ttttagtagg tatagcttgt 2220
caaagatggg gatctggaac atgaaaaata tttactaatg aaaatatgtt taaatttata 2280
ctgtgatttg acacttgcat catgtttaga tagcttaaga acaatggaag tcacagtact 2340
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gaaattgatg ttttagtttc agtgttccct atccctcatt ctccatctcc ttttgaagct 2520
cttttgaatg ttgaattgtt cataagctaa aatccaagaa atttcagctg acaacttcca 2580
aaattataat atggtatatt gccctcctgg tgtgtggctg cacacatttt atcagggaaa 2640
gttttttgat ctaggattta ttgctaacta actgaaaa 2678

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&lt;210&gt; SEQ ID NO 45

&lt;211&gt; LENGTH: 361

&lt;212&gt; TYPE: PR

&lt;213&gt; ORGANISM: Homo Sapiens

&lt;400&gt; SEQUENCE: 45

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Met Glu Ser Ile Phe His Glu Lys Gln Glu Gly Ser Leu Cys Ala Gln
1           5           10           15
His Cys Leu Asn Asn Leu Leu Gln Gly Glu Tyr Phe Ser Pro Val Glu
20          25          30
Leu Ser Ser Ile Ala His Gln Leu Asp Glu Glu Glu Arg Met Arg Met
35          40          45
Ala Glu Gly Gly Val Thr Ser Glu Asp Tyr Arg Thr Phe Leu Gln Gln
50          55          60
Pro Ser Gly Asn Met Asp Asp Ser Gly Phe Phe Ser Ile Gln Val Ile
65          70          75          80
Ser Asn Ala Leu Lys Val Trp Gly Leu Glu Leu Ile Leu Phe Asn Ser
85          90          95
Pro Glu Tyr Gln Arg Leu Arg Ile Asp Pro Ile Asn Glu Arg Ser Phe
100         105         110
Ile Cys Asn Tyr Lys Glu His Trp Phe Thr Val Arg Lys Leu Gly Lys
115        120        125
Gln Trp Phe Asn Leu Asn Ser Leu Leu Thr Gly Pro Glu Leu Ile Ser
130        135        140
Asp Thr Tyr Leu Ala Leu Phe Leu Ala Gln Leu Gln Gln Glu Gly Tyr
145        150        155        160
Ser Ile Phe Val Val Lys Gly Asp Leu Pro Asp Cys Glu Ala Asp Gln

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| 165 |     |     |     |     | 170 |     |     |     |     | 175 |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Leu | Gln | Met | Ile | Arg | Val | Gln | Gln | Met | His | Arg | Pro | Lys | Leu | Ile |
|     |     |     | 180 |     |     |     |     | 185 |     |     |     |     | 190 |     |     |
| Gly | Glu | Glu | Leu | Ala | Gln | Leu | Lys | Glu | Gln | Arg | Val | His | Lys | Thr | Asp |
|     |     |     | 195 |     |     |     | 200 |     |     |     |     | 205 |     |     |     |
| Leu | Glu | Arg | Val | Leu | Glu | Ala | Asn | Asp | Gly | Ser | Gly | Met | Leu | Asp | Glu |
|     |     |     | 210 |     |     |     | 215 |     |     |     |     | 220 |     |     |     |
| Asp | Glu | Glu | Asp | Leu | Gln | Arg | Ala | Leu | Ala | Leu | Ser | Arg | Gln | Glu | Ile |
|     |     |     | 225 |     |     |     | 230 |     |     |     |     | 235 |     |     | 240 |
| Asp | Met | Glu | Asp | Glu | Glu | Ala | Asp | Leu | Arg | Arg | Ala | Ile | Gln | Leu | Ser |
|     |     |     | 245 |     |     |     |     | 250 |     |     |     |     | 255 |     |     |
| Met | Gln | Gly | Ser | Ser | Arg | Asn | Ile | Ser | Gln | Asp | Met | Thr | Gln | Thr | Ser |
|     |     |     | 260 |     |     |     |     | 265 |     |     |     |     | 270 |     |     |
| Gly | Thr | Asn | Leu | Thr | Ser | Glu | Glu | Leu | Arg | Lys | Arg | Arg | Glu | Ala | Tyr |
|     |     |     | 275 |     |     |     | 280 |     |     |     |     | 285 |     |     |     |
| Phe | Glu | Lys | Gln | Gln | Gln | Lys | Gln | Gln | Gln | Gln | Gln | Gln | Gln | Gln | Gln |
|     |     |     | 290 |     |     |     | 295 |     |     |     |     | 300 |     |     |     |
| Gln | Gly | Asp | Leu | Ser | Gly | Gln | Ser | Ser | His | Pro | Cys | Glu | Arg | Pro | Ala |
|     |     |     | 305 |     |     |     | 310 |     |     |     |     | 315 |     |     | 320 |
| Thr | Ser | Ser | Gly | Ala | Leu | Gly | Ser | Asp | Leu | Gly | Asp | Ala | Met | Ser | Glu |
|     |     |     | 325 |     |     |     |     | 330 |     |     |     |     | 335 |     |     |
| Glu | Asp | Met | Leu | Gln | Ala | Ala | Val | Thr | Met | Ser | Leu | Glu | Thr | Val | Arg |
|     |     |     | 340 |     |     |     | 345 |     |     |     |     |     | 350 |     |     |
| Asn | Asp | Leu | Lys | Thr | Glu | Gly | Lys | Lys |     |     |     |     |     |     |     |
|     |     |     | 355 |     |     |     | 360 |     |     |     |     |     |     |     |     |

&lt;210&gt; SEQ ID NO 46

&lt;211&gt; LENGTH: 7807

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Homo Sapiens

&lt;400&gt; SEQUENCE: 46

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cgcaccctcc ttccgccctt ccttctccgg ggtcagccag gaagatgtcc cgagctgcta    60
tccccggctc ggcccgggca gccgccttct gagccccga cccgaggcgc cgagccgccc    120
ccgcccgatg ggctgggccc tggagcgtct ccgcagtcgt agctccagcc gccgcgctcc    180
cagccccggc agcctcagca tcagcggcgg cggcgggcgg ggcggcggcg tcttccgcat    240
cgttcgccgc agcgtaaccc ggagcccttt gctctttgca gaatggcccc cttcgagagc    300
gagatgccgg cccgctacgg gggaggaggc tccggggcag ccgccggggg ggtcgtgggc    360
agcggaggcg ggcgaggagc cggggggcag cggcaggggc ggcagcccgg ggcgcaaagg    420
atgtacaagc agtcaatggc gcagagagcg cggaccatgg cactctacaa ccccatcccc    480
gtccgacaga actgcctcac ggttaaccgg tctctcttcc tcttcagcga agacaacgtg    540
gtgagaaaaa acgcaaaaaa gatcaccgaa tggcctccct ttgaatatat gatttttagcc    600
accatcatag cgaattgcat cgtcctcgca ctggagcagc atctgcctga tgatgacaag    660
accccgatgt ctgaaccggc gcatgacaca gaaccatact tcattggaat tttttgtttc    720
gaggctggaa ttaaaatcat tgcccttggg tttgccttcc acaaaggtc ctacttgagg    780
aatggctgga atgtcatgga ctttgtgtgt gtgctaaccg gcactcttggc gacagttggg    840
acggagtttg acctacggac gctgagggca gttcgagtgc tgcggccgct caagctgggtg    900
tctggaatcc caagtttaca agtcgtcctg aagtcgatca tgaaggcgat gatccctttg    960
ctgcagatcg gcctcctcct attttttgca atccttattt ttgcaatcat aggggttagaa   1020

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|             |             |             |            |             |             |      |
|-------------|-------------|-------------|------------|-------------|-------------|------|
| ttttatatgg  | gaaaattttca | taccacctgc  | tttgaagagg | ggacagatga  | cattcaggggt | 1080 |
| gagtcctccg  | ctccatgtgg  | gacagaagag  | cccgcccgca | cctgccccaa  | tgggacccaa  | 1140 |
| tgtcagccct  | actgggaagg  | gcccacaac   | gggatcactc | agttcgacaa  | catcctgttt  | 1200 |
| gcagtgtga   | ctgtttttcca | gtgcataacc  | atggaagggt | ggactgatct  | cctctacaat  | 1260 |
| agcaacgatg  | cctcagggaa  | cacttggaac  | tggttgtact | tcacccccct  | catcatcacc  | 1320 |
| ggctcctttt  | ttatgctgaa  | ccttgtgtcg  | ggtgtgctgt | caggggagtt  | tgccaaagaa  | 1380 |
| agggaaacggg | tggagaaccg  | gcgggctttt  | ctgaagctga | ggcggcaaca  | acagattgaa  | 1440 |
| cgtgagctca  | atgggtacat  | ggaatggatc  | tcaaaagcag | aagagggtgat | cctcgccgag  | 1500 |
| gatgaaactg  | acggggagca  | gaggcatccc  | tttgatggag | ctctgcggag  | aaccaccata  | 1560 |
| aagaaaagca  | agacagattt  | gctcaacccc  | gaagaggctg | aggatcagct  | ggctgatata  | 1620 |
| gcctctgtgg  | gtttctccct  | cgcccgagcc  | agcattaaaa | gtgccaaact  | ggagaactcg  | 1680 |
| accttttttc  | acaaaaagga  | gaggaggatg  | cgtttctaca | tccgccgcat  | ggcaaaaact  | 1740 |
| caggccttct  | actggactgt  | actcagtttg  | gtagctctca | acacgctgtg  | tgttgctatt  | 1800 |
| gttcaactaca | accagcccca  | gtggctctcc  | gacttccttt | actatgcaga  | attcattttc  | 1860 |
| ttagactctt  | ttatgtccga  | aatgtttata  | aaaatgtacg | ggcttgggac  | gcggccttac  | 1920 |
| ttccactctt  | ccttcaactg  | ctttgactgt  | ggggttatca | ttgggagcat  | cttcgaggtc  | 1980 |
| atctgggctg  | tcataaaacc  | tggcacatcc  | tttggaatca | gcgtgttacg  | agccctcagg  | 2040 |
| ttattgcgta  | ttttcaaagt  | cacaaagtac  | tgggcatctc | tcagaaacct  | ggtcgtctct  | 2100 |
| ctcctcaact  | ccatgaagtc  | catcatcagc  | ctgttggttc | tccttttccct | gttcattgtc  | 2160 |
| gtcttcgccc  | ttttgggaat  | gcaactcttc  | ggcggccagt | ttaatttcga  | tgaagggaact | 2220 |
| cctcccacca  | acttcgatac  | ttttccagca  | gcaataatga | cgggtgtttca | gacccctgacg | 2280 |
| ggcgaagact  | ggaacgaggt  | catgtacgac  | gggatcaagt | ctcagggggg  | cgtgcagggc  | 2340 |
| ggcatgggtg  | tctccatcta  | tttcattgta  | ctgacgctct | ttgggaacta  | cacctcctcg  | 2400 |
| aatgtgttct  | tggccatcgc  | tgtggacaat  | ctggccaacg | cccaggagct  | caccaaggac  | 2460 |
| gagcaagagg  | aagaagaagc  | agcgaaccag  | aaacttgccc | tacagaaagc  | caaggagggtg | 2520 |
| gcagaagtga  | gtcctctgtc  | cgccggccaac | atgtctatag | ctgtgaaaga  | gcaacagaag  | 2580 |
| aatcaaaagc  | cagccaagtc  | cgtgtgggag  | cagcggacca | gtgagatgcg  | aaagcagaac  | 2640 |
| ttgctggcca  | gcggggagcg  | cctgtataac  | gaaatggacc | cggacgagcg  | ctggaaggct  | 2700 |
| gcctacacgc  | ggcacctcgc  | gccagacatg  | aagacgcact | tggaccggcc  | gctggtggtg  | 2760 |
| gaccgcgagg  | agaaccgcaa  | caacaacacc  | aacaagagcc | gggcggccga  | gcccaccgtg  | 2820 |
| gaccagcgcc  | tcggccagca  | gcgcgccgag  | gacttcctca | ggaaacaggc  | ccgctaccac  | 2880 |
| gacggggccc  | gggaccccag  | cggctcggcg  | ggcctggacg | cacggaggcc  | ctgggcggga  | 2940 |
| agccaggagg  | ccgagctgag  | ccgggaggga  | ccctacggcc | gcgagtcgga  | ccaccacgcc  | 3000 |
| cgggagggca  | gcctggagca  | acccgggttc  | tgggaggcg  | aggccgagcg  | aggcaaggcc  | 3060 |
| ggggaccccc  | accggaggca  | cgtgcaccgg  | caggggggca | gcagggagag  | ccgcagcggg  | 3120 |
| tccccgcgca  | cgggcgcgga  | cggggagcat  | cgacgtcatc | gcgcgcaccg  | cagggcccggg | 3180 |
| gaggagggtc  | cggaggacaa  | ggcggagcgg  | agggcgcggc | accgcgaggg  | cagccggccg  | 3240 |
| gccccggggcg | gcgagggcgga | gggcgagggc  | cccgcagggg | gcgagcgag   | gagaaggcac  | 3300 |
| cggcatggcg  | ctccagccac  | gtacgagggg  | gacgcgcgga | gggaggacaa  | ggagcggagg  | 3360 |
| catcggagga  | ggaaagagaa  | ccagggctcc  | ggggtccctg | tgtcggggccc | caacctgtca  | 3420 |

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|                                                                    |      |
|--------------------------------------------------------------------|------|
| accaccggc caatccagca ggacctgggc cgccaagacc caccctggc agaggatatt    | 3480 |
| gacaacatga agaacaacaa gctggccacc gcgagtcgg ccgtcccca cggcagcctt    | 3540 |
| ggccacgcc gcttgccca gagccagcc aagatgggaa acagcacga ccccgcccc       | 3600 |
| atgctggcca tcctgccat ggccaccaac cccagaacg ccgccagccg ccggacgccc    | 3660 |
| aacaaccgg ggaaccatc caatccggc cccccaaga ccccgagaa tagccttate       | 3720 |
| gtcaccaacc ccagcggcac ccagaccaat tcagctaaga ctgccaggaa acccgaccac  | 3780 |
| accacagtgg acatccccc agcctgcccc ccccccctca accacaccgt cgtacaagtg   | 3840 |
| aacaaaaacg ccaaccaga cccactgcca aaaaaagagg aagagaagaa ggaggaggag   | 3900 |
| gaagacgacc gtgggaaga cggccctaag ccaatgcctc cctatagctc catgttcac    | 3960 |
| ctgtccacga ccaacccct tcgcccctg tgccattaca tcctgaacct gcgctacttt    | 4020 |
| gagatgtgca tcctcatggt cattgccatg agcagcatcg cctggccgc cgaggaccct   | 4080 |
| gtgcagccca acgcacctg gaacaacgtg ctgcgatact ttgactacgt tttacaggc    | 4140 |
| gtctttacct ttgagatggt gatcaagatg attgacctgg ggctcgtcct gcacagggg   | 4200 |
| gcctacttcc gtgacctctg gaatatctc gacttcacag tggtcagtgg ggccctggta   | 4260 |
| gcctttgcct tccctggcaa tagcaaaagg aaagacatca acacgattaa atccctccga  | 4320 |
| gtcctccggg tgctacgacc tcttaaaacc atcaagcggc tgccaaagct caaggctgtg  | 4380 |
| tttgactgtg tgggaacct acttaaaac gtcttcaaca tcctcatcgt ctacatgcta    | 4440 |
| ttcatgttca tcttcgccg ggtggctgtg cagctcttca aggggaaatt cttccactgc   | 4500 |
| actgacgagt ccaaagagt tgagaaagat tgcgaggca aatacctcct ctacgagaag    | 4560 |
| aatgagggtga aggcgcgaga cggggagtgg aagaagtatg aattccatta cgacaatgtg | 4620 |
| ctgtgggctc tgcagacct cttcacctg tccacgggag aaggctggcc acaggctcctc   | 4680 |
| aagcattcgg tggacgccac ctttgagaac cagggcccca gcccgggta ccgcatggag   | 4740 |
| atgtccattt tctacgtcgt ctactttgtg gtgttccct tcttctttgt caatatcttt   | 4800 |
| gtggccttga tcatcatcac cttccaggag caaggggaca agatgatgga ggaatacagc  | 4860 |
| ctggagaaaa atgagagggc ctgcattgat ttcgccatca gcgccagcc gctgacccga   | 4920 |
| cacatgccgc agaacaagca gagcttcag tacccgatgt ggcagttcgt ggtgtctccg   | 4980 |
| cctttcagat acacgatcat ggccatgac gccctcaaca ccatcgtgct tatgatgaag   | 5040 |
| ttctatggg cttctgttgc ttatgaaaat gccctgcggg tgttcaacat cgtcttcacc   | 5100 |
| tccctcttct ctctggaatg tgtgctgaaa gtcatggctt ttgggattct gaattatttc  | 5160 |
| cgcatgcct ggaacatctt cgactttgtg actgttctgg gcagcatcac cgatatectc   | 5220 |
| gtgactgagt ttgggaataa cttcatcaac ctgagcttcc tccgcctctt ccgagctgcc  | 5280 |
| cggctcatca aacttctccg tcagggttac accatccgca ttcttctctg gacctttgtg  | 5340 |
| cagtccttca aggcctgcc ttatgtctgt ctgctgatcg ccatgctctt cttcatctat   | 5400 |
| gccatcattg ggatgcagg gtttggtaac attggcatcg acgtggagga cgaggacagt   | 5460 |
| gatgaagatg agttccaaat cactgagcac aataacttcc ggaccttctt ccaggccctc  | 5520 |
| atgcttctct tccgagtgcc caccggggaa gcttggcaca acatcatgct ttctgcctc   | 5580 |
| agcgggaaac cgtgtgataa gaactctggc atcctgactc gagagtgtgg caatgaattt  | 5640 |
| gcttattttt actttgttcc cttcatcttc ctctgctcgt ttctgatgct gaatctcttt  | 5700 |
| gtcgcgtca tcatggacaa ctttgagtac ctcacccgag actcctccat cctgggcccc   | 5760 |
| caccacctgg atgagtacgt gcgtgtctgg gccgagtatg accccgcagc ttgcggtcgg  | 5820 |

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attcattata aggatatgta cagtttatta cgagtaatat ctccccctct cggtcttaggc 5880
aagaaatgtc ctcatagggt tgcttgcaag cggcttctgc ggatggacct gcccgctgca 5940
gatgacaaca ccgtccactt caattccacc ctcatggctc tgatccgcac agccctggac 6000
atcaagattg ccaaggagg agccgacaaa cagcagatgg acgctgagct gcggaaggag 6060
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gagatgcgag agatgggcag agatgggtac tccgacagcg agcactacct ccccatggaa 6540
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cgccacgtg ggaataacct cagtaccatc tcagacacca gccccatgaa gcgttcagcc 6660
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gaggagaacc agcggcacca ccagcggcgc cgcgaccgca gccaccgccc ctctgagcgc 6780
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caatccgggg acctgcctgc gaaggagcgg gaccaggagc ggggccggcc caaggatcgg 6900
aagcatcgac agcaccacca ccaccaccac caccaccacc atcccccgcc ccccgacaag 6960
gaccgctatg cccaggaacg gccggaccac ggccggggcac gggctcggga ccagcgtgg 7020
tcccgcctgc ccagcaggg ccgagagcac atggcgacac ggcagtagtt ccgtaagtgg 7080
aagcccagcc ccctcaacat ctggtaccag cactccgcgg cggggccgcc gccagctccc 7140
ccagaccccc tccaccccc ggccacacgt gtctatttc cctgtgatcc gtaaggccgg 7200
cggtcgggg cccccgcagc agcagcagca gcagcagcag cagcagcagg cggtggccag 7260
gccgggccc ggcggccacca gcggccctcg gaggtacca gggccacagg ccgagcctct 7320
ggccggagat cggccgcccc cggggggcca cagcagcggc cgctcgcccc ggatggagag 7380
gcgggtccca gggccggccc ggagcagtc cccaggggcc tgtcgacac gcggggccc 7440
gtggccggca tctggcccgc acgtgtccga ggggcccccg ggtccccggc accatggcta 7500
ctaccggggc tccgactacg acgaggccga tggcccgggc agcggggggc gcgaggaggc 7560
catggccggg gcctacgacg cgccaccccc cgtacgacac gcgtcctcgg gcgccaccgg 7620
gcgtcgcgcc aggaactccc gggcctcggg cccggcctgc gcctcgcctt ctcggcacgg 7680
ccggcgactc cccaacggct actaccggc gcacggactg gccaggcccc gcgggcccgg 7740
ctccaggaag ggctgcacg aaccctacg cgagagtac gatgattggt gctaagcccc 7800
ggcgagg 7807

```

&lt;210&gt; SEQ ID NO 47

&lt;211&gt; LENGTH: 2261

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Homo Sapiens

&lt;400&gt; SEQUENCE: 47

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Met Ala Arg Phe Gly Asp Glu Met Pro Ala Arg Tyr Gly Gly Gly Gly
1           5           10          15

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Ser Gly Ala Ala Ala Gly Val Val Val Gly Ser Gly Gly Gly Arg Gly

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|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |  |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|--|
| 20  |     |     |     |     |     | 25  |     |     |     |     |     | 30  |     |     |     |  |  |
| Ala | Gly | Gly | Ser | Arg | Gln | Gly | Gly | Gln | Pro | Gly | Ala | Gln | Arg | Met | Tyr |  |  |
|     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |  |  |
| Lys | Gln | Ser | Met | Ala | Gln | Arg | Ala | Arg | Thr | Met | Ala | Leu | Tyr | Asn | Pro |  |  |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |  |  |
| Ile | Pro | Val | Arg | Gln | Asn | Cys | Leu | Thr | Val | Asn | Arg | Ser | Leu | Phe | Leu |  |  |
| 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |  |  |
| Phe | Ser | Glu | Asp | Asn | Val | Val | Arg | Lys | Tyr | Ala | Lys | Lys | Ile | Thr | Glu |  |  |
|     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |  |  |
| Trp | Pro | Pro | Phe | Glu | Tyr | Met | Ile | Leu | Ala | Thr | Ile | Ile | Ala | Asn | Cys |  |  |
|     |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |  |  |
| Ile | Val | Leu | Ala | Leu | Glu | Gln | His | Leu | Pro | Asp | Asp | Asp | Lys | Thr | Pro |  |  |
|     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |  |  |
| Met | Ser | Glu | Arg | Leu | Asp | Asp | Thr | Glu | Pro | Tyr | Phe | Ile | Gly | Ile | Phe |  |  |
|     | 130 |     |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |  |  |
| Cys | Phe | Glu | Ala | Gly | Ile | Lys | Ile | Ile | Ala | Leu | Gly | Phe | Ala | Phe | His |  |  |
| 145 |     |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     | 160 |  |  |
| Lys | Gly | Ser | Tyr | Leu | Arg | Asn | Gly | Trp | Asn | Val | Met | Asp | Phe | Val | Val |  |  |
|     |     |     |     | 165 |     |     |     |     | 170 |     |     |     |     | 175 |     |  |  |
| Val | Leu | Thr | Gly | Ile | Leu | Ala | Thr | Val | Gly | Thr | Glu | Phe | Asp | Leu | Arg |  |  |
|     |     |     | 180 |     |     |     |     | 185 |     |     |     |     | 190 |     |     |  |  |
| Thr | Leu | Arg | Ala | Val | Arg | Val | Leu | Arg | Pro | Leu | Lys | Leu | Val | Ser | Gly |  |  |
|     |     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |  |  |
| Ile | Pro | Ser | Leu | Gln | Val | Val | Leu | Lys | Ser | Ile | Met | Lys | Ala | Met | Ile |  |  |
|     | 210 |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |  |  |
| Pro | Leu | Leu | Gln | Ile | Gly | Leu | Leu | Leu | Phe | Phe | Ala | Ile | Leu | Ile | Phe |  |  |
| 225 |     |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |  |  |
| Ala | Ile | Ile | Gly | Leu | Glu | Phe | Tyr | Met | Gly | Lys | Phe | His | Thr | Thr | Cys |  |  |
|     |     |     |     | 245 |     |     |     |     | 250 |     |     |     |     | 255 |     |  |  |
| Phe | Glu | Glu | Gly | Thr | Asp | Asp | Ile | Gln | Gly | Glu | Ser | Pro | Ala | Pro | Cys |  |  |
|     |     |     | 260 |     |     |     |     | 265 |     |     |     |     | 270 |     |     |  |  |
| Gly | Thr | Glu | Glu | Pro | Ala | Arg | Thr | Cys | Pro | Asn | Gly | Thr | Lys | Cys | Gln |  |  |
|     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |  |  |
| Pro | Tyr | Trp | Glu | Gly | Pro | Asn | Asn | Gly | Ile | Thr | Gln | Phe | Asp | Asn | Ile |  |  |
|     | 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |  |  |
| Leu | Phe | Ala | Val | Leu | Thr | Val | Phe | Gln | Cys | Ile | Thr | Met | Glu | Gly | Trp |  |  |
| 305 |     |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |  |  |
| Thr | Asp | Leu | Leu | Tyr | Asn | Ser | Asn | Asp | Ala | Ser | Gly | Asn | Thr | Trp | Asn |  |  |
|     |     |     |     | 325 |     |     |     |     | 330 |     |     |     |     | 335 |     |  |  |
| Trp | Leu | Tyr | Phe | Ile | Pro | Leu | Ile | Ile | Ile | Gly | Ser | Phe | Phe | Met | Leu |  |  |
|     |     |     | 340 |     |     |     |     | 345 |     |     |     |     | 350 |     |     |  |  |
| Asn | Leu | Val | Leu | Gly | Val | Leu | Ser | Gly | Glu | Phe | Ala | Lys | Glu | Arg | Glu |  |  |
|     |     | 355 |     |     |     |     | 360 |     |     |     |     | 365 |     |     |     |  |  |
| Arg | Val | Glu | Asn | Arg | Arg | Ala | Phe | Leu | Lys | Leu | Arg | Arg | Gln | Gln | Gln |  |  |
|     | 370 |     |     |     |     | 375 |     |     |     |     | 380 |     |     |     |     |  |  |
| Ile | Glu | Arg | Glu | Leu | Asn | Gly | Tyr | Met | Glu | Trp | Ile | Ser | Lys | Ala | Glu |  |  |
| 385 |     |     |     |     | 390 |     |     |     |     | 395 |     |     |     |     | 400 |  |  |
| Glu | Val | Ile | Leu | Ala | Glu | Asp | Glu | Thr | Asp | Gly | Glu | Gln | Arg | His | Pro |  |  |
|     |     |     | 405 |     |     |     |     |     | 410 |     |     |     |     | 415 |     |  |  |
| Phe | Asp | Gly | Ala | Leu | Arg | Arg | Thr | Thr | Ile | Lys | Lys | Ser | Lys | Thr | Asp |  |  |
|     |     |     | 420 |     |     |     |     | 425 |     |     |     |     | 430 |     |     |  |  |
| Leu | Leu | Asn | Pro | Glu | Glu | Ala | Glu | Asp | Gln | Leu | Ala | Asp | Ile | Ala | Ser |  |  |
|     |     | 435 |     |     |     |     | 440 |     |     |     |     | 445 |     |     |     |  |  |

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|                                                                 |  |
|-----------------------------------------------------------------|--|
| Val Gly Ser Pro Phe Ala Arg Ala Ser Ile Lys Ser Ala Lys Leu Glu |  |
| 450 455 460                                                     |  |
| Asn Ser Thr Phe Phe His Lys Lys Glu Arg Arg Met Arg Phe Tyr Ile |  |
| 465 470 475 480                                                 |  |
| Arg Arg Met Val Lys Thr Gln Ala Phe Tyr Trp Thr Val Leu Ser Leu |  |
| 485 490 495                                                     |  |
| Val Ala Leu Asn Thr Leu Cys Val Ala Ile Val His Tyr Asn Gln Pro |  |
| 500 505 510                                                     |  |
| Glu Trp Leu Ser Asp Phe Leu Tyr Tyr Ala Glu Phe Ile Phe Leu Gly |  |
| 515 520 525                                                     |  |
| Leu Phe Met Ser Glu Met Phe Ile Lys Met Tyr Gly Leu Gly Thr Arg |  |
| 530 535 540                                                     |  |
| Pro Tyr Phe His Ser Ser Phe Asn Cys Phe Asp Cys Gly Val Ile Ile |  |
| 545 550 555 560                                                 |  |
| Gly Ser Ile Phe Glu Val Ile Trp Ala Val Ile Lys Pro Gly Thr Ser |  |
| 565 570 575                                                     |  |
| Phe Gly Ile Ser Val Leu Arg Ala Leu Arg Leu Leu Arg Ile Phe Lys |  |
| 580 585 590                                                     |  |
| Val Thr Lys Tyr Trp Ala Ser Leu Arg Asn Leu Val Val Ser Leu Leu |  |
| 595 600 605                                                     |  |
| Asn Ser Met Lys Ser Ile Ile Ser Leu Leu Phe Leu Leu Phe Leu Phe |  |
| 610 615 620                                                     |  |
| Ile Val Val Phe Ala Leu Leu Gly Met Gln Leu Phe Gly Gly Gln Phe |  |
| 625 630 635 640                                                 |  |
| Asn Phe Asp Glu Gly Thr Pro Pro Thr Asn Phe Asp Thr Phe Pro Ala |  |
| 645 650 655                                                     |  |
| Ala Ile Met Thr Val Phe Gln Ile Leu Thr Gly Glu Asp Trp Asn Glu |  |
| 660 665 670                                                     |  |
| Val Met Tyr Asp Gly Ile Lys Ser Gln Gly Gly Val Gln Gly Gly Met |  |
| 675 680 685                                                     |  |
| Val Phe Ser Ile Tyr Phe Ile Val Leu Thr Leu Phe Gly Asn Tyr Thr |  |
| 690 695 700                                                     |  |
| Leu Leu Asn Val Phe Leu Ala Ile Ala Val Asp Asn Leu Ala Asn Ala |  |
| 705 710 715 720                                                 |  |
| Gln Glu Leu Thr Lys Asp Glu Gln Glu Glu Glu Ala Ala Asn Gln     |  |
| 725 730 735                                                     |  |
| Lys Leu Ala Leu Gln Lys Ala Lys Glu Val Ala Glu Val Ser Pro Leu |  |
| 740 745 750                                                     |  |
| Ser Ala Ala Asn Met Ser Ile Ala Val Lys Glu Gln Gln Lys Asn Gln |  |
| 755 760 765                                                     |  |
| Lys Pro Ala Lys Ser Val Trp Glu Gln Arg Thr Ser Glu Met Arg Lys |  |
| 770 775 780                                                     |  |
| Gln Asn Leu Leu Ala Ser Arg Glu Ala Leu Tyr Asn Glu Met Asp Pro |  |
| 785 790 795 800                                                 |  |
| Asp Glu Arg Trp Lys Ala Ala Tyr Thr Arg His Leu Arg Pro Asp Met |  |
| 805 810 815                                                     |  |
| Lys Thr His Leu Asp Arg Pro Leu Val Val Asp Pro Gln Glu Asn Arg |  |
| 820 825 830                                                     |  |
| Asn Asn Asn Thr Asn Lys Ser Arg Ala Ala Glu Pro Thr Val Asp Gln |  |
| 835 840 845                                                     |  |
| Arg Leu Gly Gln Gln Arg Ala Glu Asp Phe Leu Arg Lys Gln Ala Arg |  |
| 850 855 860                                                     |  |
| Tyr His Asp Arg Ala Arg Asp Pro Ser Gly Ser Ala Gly Leu Asp Ala |  |
| 865 870 875 880                                                 |  |

|     |      |     |     |     |     |      |      |     |     |     |      |      |     |     |     |  |
|-----|------|-----|-----|-----|-----|------|------|-----|-----|-----|------|------|-----|-----|-----|--|
| Arg | Arg  | Pro | Trp | Ala | Gly | Ser  | Gln  | Glu | Ala | Glu | Leu  | Ser  | Arg | Glu | Gly |  |
|     |      |     |     | 885 |     |      |      |     | 890 |     |      |      |     | 895 |     |  |
| Pro | Tyr  | Gly | Arg | Glu | Ser | Asp  | His  | His | Ala | Arg | Glu  | Gly  | Ser | Leu | Glu |  |
|     |      |     | 900 |     |     |      |      | 905 |     |     |      |      | 910 |     |     |  |
| Gln | Pro  | Gly | Phe | Trp | Glu | Gly  | Glu  | Ala | Glu | Arg | Gly  | Lys  | Ala | Gly | Asp |  |
|     |      |     | 915 |     |     |      | 920  |     |     |     |      | 925  |     |     |     |  |
| Pro | His  | Arg | Arg | His | Val | His  | Arg  | Gln | Gly | Gly | Ser  | Arg  | Glu | Ser | Arg |  |
|     |      |     |     |     |     | 935  |      |     |     |     | 940  |      |     |     |     |  |
| Ser | Gly  | Ser | Pro | Arg | Thr | Gly  | Ala  | Asp | Gly | Glu | His  | Arg  | Arg | His | Arg |  |
| 945 |      |     |     |     | 950 |      |      |     |     | 955 |      |      |     | 960 |     |  |
| Ala | His  | Arg | Arg | Pro | Gly | Glu  | Glu  | Gly | Pro | Glu | Asp  | Lys  | Ala | Glu | Arg |  |
|     |      |     |     | 965 |     |      |      |     | 970 |     |      |      |     | 975 |     |  |
| Arg | Ala  | Arg | His | Arg | Glu | Gly  | Ser  | Arg | Pro | Ala | Arg  | Gly  | Gly | Glu | Gly |  |
|     |      |     | 980 |     |     |      |      | 985 |     |     |      |      | 990 |     |     |  |
| Glu | Gly  | Glu | Gly | Pro | Asp | Gly  | Gly  | Glu | Arg | Arg | Arg  | Arg  | His | Arg | His |  |
|     |      |     | 995 |     |     |      | 1000 |     |     |     |      | 1005 |     |     |     |  |
| Gly | Ala  | Pro | Ala | Thr | Tyr | Glu  | Gly  | Asp | Ala | Arg | Arg  | Arg  | Glu | Asp | Lys |  |
|     | 1010 |     |     |     |     | 1015 |      |     |     |     |      | 1020 |     |     |     |  |
| Glu | Arg  | Arg | His | Arg | Arg | Arg  | Lys  | Glu | Asn | Gln | Gly  | Ser  | Gly | Val |     |  |
|     | 1025 |     |     |     |     | 1030 |      |     |     |     |      | 1035 |     |     |     |  |
| Pro | Val  | Ser | Gly | Pro | Asn | Leu  | Ser  | Thr | Thr | Arg | Pro  | Ile  | Gln | Gln |     |  |
|     | 1040 |     |     |     |     | 1045 |      |     |     |     | 1050 |      |     |     |     |  |
| Asp | Leu  | Gly | Arg | Gln | Asp | Pro  | Pro  | Leu | Ala | Glu | Asp  | Ile  | Asp | Asn |     |  |
|     | 1055 |     |     |     |     | 1060 |      |     |     |     | 1065 |      |     |     |     |  |
| Met | Lys  | Asn | Asn | Lys | Leu | Ala  | Thr  | Ala | Glu | Ser | Ala  | Ala  | Pro | His |     |  |
|     | 1070 |     |     |     |     | 1075 |      |     |     |     | 1080 |      |     |     |     |  |
| Gly | Ser  | Leu | Gly | His | Ala | Gly  | Leu  | Pro | Gln | Ser | Pro  | Ala  | Lys | Met |     |  |
|     | 1085 |     |     |     |     | 1090 |      |     |     |     | 1095 |      |     |     |     |  |
| Gly | Asn  | Ser | Thr | Asp | Pro | Gly  | Pro  | Met | Leu | Ala | Ile  | Pro  | Ala | Met |     |  |
|     | 1100 |     |     |     |     | 1105 |      |     |     |     | 1110 |      |     |     |     |  |
| Ala | Thr  | Asn | Pro | Gln | Asn | Ala  | Ala  | Ser | Arg | Arg | Thr  | Pro  | Asn | Asn |     |  |
|     | 1115 |     |     |     |     | 1120 |      |     |     |     | 1125 |      |     |     |     |  |
| Pro | Gly  | Asn | Pro | Ser | Asn | Pro  | Gly  | Pro | Pro | Lys | Thr  | Pro  | Glu | Asn |     |  |
|     | 1130 |     |     |     |     | 1135 |      |     |     |     | 1140 |      |     |     |     |  |
| Ser | Leu  | Ile | Val | Thr | Asn | Pro  | Ser  | Gly | Thr | Gln | Thr  | Asn  | Ser | Ala |     |  |
|     | 1145 |     |     |     |     | 1150 |      |     |     |     | 1155 |      |     |     |     |  |
| Lys | Thr  | Ala | Arg | Lys | Pro | Asp  | His  | Thr | Thr | Val | Asp  | Ile  | Pro | Pro |     |  |
|     | 1160 |     |     |     |     | 1165 |      |     |     |     | 1170 |      |     |     |     |  |
| Ala | Cys  | Pro | Pro | Pro | Leu | Asn  | His  | Thr | Val | Val | Gln  | Val  | Asn | Lys |     |  |
|     | 1175 |     |     |     |     | 1180 |      |     |     |     | 1185 |      |     |     |     |  |
| Asn | Ala  | Asn | Pro | Asp | Pro | Leu  | Pro  | Lys | Lys | Glu | Glu  | Glu  | Lys | Lys |     |  |
|     | 1190 |     |     |     |     | 1195 |      |     |     |     | 1200 |      |     |     |     |  |
| Glu | Glu  | Glu | Glu | Asp | Asp | Arg  | Gly  |     |     |     |      |      |     |     |     |  |

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| 1280                        | 1285                            | 1290 |
|-----------------------------|---------------------------------|------|
| Ile Lys Met Ile Asp Leu Gly | Leu Val Leu His Gln Gly Ala Tyr |      |
| 1295                        | 1300                            | 1305 |
| Phe Arg Asp Leu Trp Asn Ile | Leu Asp Phe Ile Val Val Ser Gly |      |
| 1310                        | 1315                            | 1320 |
| Ala Leu Val Ala Phe Ala Phe | Thr Gly Asn Ser Lys Gly Lys Asp |      |
| 1325                        | 1330                            | 1335 |
| Ile Asn Thr Ile Lys Ser Leu | Arg Val Leu Arg Val Leu Arg Pro |      |
| 1340                        | 1345                            | 1350 |
| Leu Lys Thr Ile Lys Arg Leu | Pro Lys Leu Lys Ala Val Phe Asp |      |
| 1355                        | 1360                            | 1365 |
| Cys Val Val Asn Ser Leu Lys | Asn Val Phe Asn Ile Leu Ile Val |      |
| 1370                        | 1375                            | 1380 |
| Tyr Met Leu Phe Met Phe Ile | Phe Ala Val Val Ala Val Gln Leu |      |
| 1385                        | 1390                            | 1395 |
| Phe Lys Gly Lys Phe Phe His | Cys Thr Asp Glu Ser Lys Glu Phe |      |
| 1400                        | 1405                            | 1410 |
| Glu Lys Asp Cys Arg Gly Lys | Tyr Leu Leu Tyr Glu Lys Asn Glu |      |
| 1415                        | 1420                            | 1425 |
| Val Lys Ala Arg Asp Arg Glu | Trp Lys Lys Tyr Glu Phe His Tyr |      |
| 1430                        | 1435                            | 1440 |
| Asp Asn Val Leu Trp Ala Leu | Leu Thr Leu Phe Thr Val Ser Thr |      |
| 1445                        | 1450                            | 1455 |
| Gly Glu Gly Trp Pro Gln Val | Leu Lys His Ser Val Asp Ala Thr |      |
| 1460                        | 1465                            | 1470 |
| Phe Glu Asn Gln Gly Pro Ser | Pro Gly Tyr Arg Met Glu Met Ser |      |
| 1475                        | 1480                            | 1485 |
| Ile Phe Tyr Val Val Tyr Phe | Val Val Phe Pro Phe Phe Phe Val |      |
| 1490                        | 1495                            | 1500 |
| Asn Ile Phe Val Ala Leu Ile | Ile Ile Thr Phe Gln Glu Gln Gly |      |
| 1505                        | 1510                            | 1515 |
| Asp Lys Met Met Glu Glu Tyr | Ser Leu Glu Lys Asn Glu Arg Ala |      |
| 1520                        | 1525                            | 1530 |
| Cys Ile Asp Phe Ala Ile Ser | Ala Lys Pro Leu Thr Arg His Met |      |
| 1535                        | 1540                            | 1545 |
| Pro Gln Asn Lys Gln Ser Phe | Gln Tyr Arg Met Trp Gln Phe Val |      |
| 1550                        | 1555                            | 1560 |
| Val Ser Pro Pro Phe Glu Tyr | Thr Ile Met Ala Met Ile Ala Leu |      |
| 1565                        | 1570                            | 1575 |
| Asn Thr Ile Val Leu Met Met | Lys Phe Tyr Gly Ala Ser Val Ala |      |
| 1580                        | 1585                            | 1590 |
| Tyr Glu Asn Ala Leu Arg Val | Phe Asn Ile Val Phe Thr Ser Leu |      |
| 1595                        | 1600                            | 1605 |
| Phe Ser Leu Glu Cys Val Leu | Lys Val Met Ala Phe Gly Ile Leu |      |
| 1610                        | 1615                            | 1620 |
| Asn Tyr Phe Arg Asp Ala Trp | Asn Ile Phe Asp Phe Val Thr Val |      |
| 1625                        | 1630                            | 1635 |
| Leu Gly Ser Ile Thr Asp Ile | Leu Val Thr Glu Phe Gly Asn Asn |      |
| 1640                        | 1645                            | 1650 |
| Phe Ile Asn Leu Ser Phe Leu | Arg Leu Phe Arg Ala Ala Arg Leu |      |
| 1655                        | 1660                            | 1665 |
| Ile Lys Leu Leu Arg Gln Gly | Tyr Thr Ile Arg Ile Leu Leu Trp |      |
| 1670                        | 1675                            | 1680 |

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|         |                 |      |                 |      |             |
|---------|-----------------|------|-----------------|------|-------------|
| Thr Phe | Val Gln Ser Phe | Lys  | Ala Leu Pro Tyr | Val  | Cys Leu Leu |
| 1685    |                 | 1690 |                 | 1695 |             |
| Ile Ala | Met Leu Phe Phe | Ile  | Tyr Ala Ile Ile | Gly  | Met Gln Val |
| 1700    |                 | 1705 |                 | 1710 |             |
| Phe Gly | Asn Ile Gly Ile | Asp  | Val Glu Asp Glu | Asp  | Ser Asp Glu |
| 1715    |                 | 1720 |                 | 1725 |             |
| Asp Glu | Phe Gln Ile Thr | Glu  | His Asn Asn Phe | Arg  | Thr Phe Phe |
| 1730    |                 | 1735 |                 | 1740 |             |
| Gln Ala | Leu Met Leu Leu | Phe  | Arg Ser Ala Thr | Gly  | Glu Ala Trp |
| 1745    |                 | 1750 |                 | 1755 |             |
| His Asn | Ile Met Leu Ser | Cys  | Leu Ser Gly Lys | Pro  | Cys Asp Lys |
| 1760    |                 | 1765 |                 | 1770 |             |
| Asn Ser | Gly Ile Leu Thr | Arg  | Glu Cys Gly Asn | Glu  | Phe Ala Tyr |
| 1775    |                 | 1780 |                 | 1785 |             |
| Phe Tyr | Phe Val Ser Phe | Ile  | Phe Leu Cys Ser | Phe  | Leu Met Leu |
| 1790    |                 | 1795 |                 | 1800 |             |
| Asn Leu | Phe Val Ala Val | Ile  | Met Asp Asn Phe | Glu  | Tyr Leu Thr |
| 1805    |                 | 1810 |                 | 1815 |             |
| Arg Asp | Ser Ser Ile Leu | Gly  | Pro His His Leu | Asp  | Glu Tyr Val |
| 1820    |                 | 1825 |                 | 1830 |             |
| Arg Val | Trp Ala Glu Tyr | Asp  | Pro Ala Ala Cys | Gly  | Arg Ile His |
| 1835    |                 | 1840 |                 | 1845 |             |
| Tyr Lys | Asp Met Tyr Ser | Leu  | Leu Arg Val Ile | Ser  | Pro Pro Leu |
| 1850    |                 | 1855 |                 | 1860 |             |
| Gly Leu | Gly Lys Lys Cys | Pro  | His Arg Val Ala | Cys  | Lys Arg Leu |
| 1865    |                 | 1870 |                 | 1875 |             |
| Leu Arg | Met Asp Leu Pro | Val  | Ala Asp Asp Asn | Thr  | Val His Phe |
| 1880    |                 | 1885 |                 | 1890 |             |
| Asn Ser | Thr Leu Met Ala | Leu  | Ile Arg Thr Ala | Leu  | Asp Ile Lys |
| 1895    |                 | 1900 |                 | 1905 |             |
| Ile Ala | Lys Gly Gly Ala | Asp  | Lys Gln Gln Met | Asp  | Ala Glu Leu |
| 1910    |                 | 1915 |                 | 1920 |             |
| Arg Lys | Glu Met Met Ala | Ile  | Trp Pro Asn Leu | Ser  | Gln Lys Thr |
| 1925    |                 | 1930 |                 | 1935 |             |
| Leu Asp | Leu Leu Val Thr | Pro  | His Lys Ser Thr | Asp  | Leu Thr Val |
| 1940    |                 | 1945 |                 | 1950 |             |
| Gly Lys | Ile Tyr Ala Ala | Met  | Met Ile Met Glu | Tyr  | Tyr Arg Gln |
| 1955    |                 | 1960 |                 | 1965 |             |
| Ser Lys | Ala Lys Lys Leu | Gln  | Ala Met Arg Glu | Glu  | Gln Asp Arg |
| 1970    |                 | 1975 |                 | 1980 |             |
| Thr Pro | Leu Met Phe Gln | Arg  | Met Glu Pro Pro | Ser  | Pro Thr Gln |
| 1985    |                 | 1990 |                 | 1995 |             |
| Glu Gly | Gly Pro Gly Gln | Asn  | Ala Leu Pro Ser | Thr  | Gln Leu Asp |
| 2000    |                 | 2005 |                 | 2010 |             |
| Pro Gly | Gly Ala Leu Met | Ala  | His Glu Ser Gly | Leu  | Lys Glu Ser |
| 2015    |                 | 2020 |                 | 2025 |             |
| Pro Ser | Trp Val Thr Gln | Arg  | Ala Gln Glu Met | Phe  | Gln Lys Thr |
| 2030    |                 | 2035 |                 | 2040 |             |
| Gly Thr | Trp Ser Pro Glu | Gln  | Gly Pro Pro Thr | Asp  | Met Pro Asn |
| 2045    |                 | 2050 |                 | 2055 |             |
| Ser Gln | Pro Asn Ser Gln | Ser  | Val Glu Met Arg | Glu  | Met Gly Arg |
| 2060    |                 | 2065 |                 | 2070 |             |
| Asp Gly | Tyr Ser Asp Ser | Glu  | His Tyr Leu Pro | Met  | Glu Gly Gln |
| 2075    |                 | 2080 |                 | 2085 |             |

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Gly Arg Ala Ala Ser Met Pro Arg Leu Pro Ala Glu Asn Gln Arg  
 2090 2095 2100  
 Arg Arg Gly Arg Pro Arg Gly Asn Asn Leu Ser Thr Ile Ser Asp  
 2105 2110 2115  
 Thr Ser Pro Met Lys Arg Ser Ala Ser Val Leu Gly Pro Lys Ala  
 2120 2125 2130  
 Arg Arg Leu Asp Asp Tyr Ser Leu Glu Arg Val Pro Pro Glu Glu  
 2135 2140 2145  
 Asn Gln Arg His His Gln Arg Arg Arg Asp Arg Ser His Arg Ala  
 2150 2155 2160  
 Ser Glu Arg Ser Leu Gly Arg Tyr Thr Asp Val Asp Thr Gly Leu  
 2165 2170 2175  
 Gly Thr Asp Leu Ser Met Thr Thr Gln Ser Gly Asp Leu Pro Ser  
 2180 2185 2190  
 Lys Glu Arg Asp Gln Glu Arg Gly Arg Pro Lys Asp Arg Lys His  
 2195 2200 2205  
 Arg Gln His His His His His His His His His Pro Pro Pro  
 2210 2215 2220  
 Pro Asp Lys Asp Arg Tyr Ala Gln Glu Arg Pro Asp His Gly Arg  
 2225 2230 2235  
 Ala Arg Ala Arg Asp Gln Arg Trp Ser Arg Ser Pro Ser Glu Gly  
 2240 2245 2250  
 Arg Glu His Met Ala His Arg Gln  
 2255 2260

&lt;210&gt; SEQ ID NO 48

&lt;211&gt; LENGTH: 4416

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Homo Sapiens

&lt;400&gt; SEQUENCE: 48

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gaaaaagggt gaaagagaaa cttggcgacc tcccgaggga gttcgcgaag cgaccaggag      60
cgtgttgcca tcgtcctcac ccggcaccca attccaccac agatcgggga tttcgtcggt      120
gatcgtgatg ggggtccttt attttctctc ttgattttca aaaaatgtct atgtgactgt      180
ccctatctta aggggaagtt gaaagtgggg gcgggggtgc tcaatgagaa acgttgccct      240
gtgtgtagtt gtttgaggca cactgcaaat tatattggca tctctttcca aaagtcactt      300
tgattcaact tcgatagctt tctcgtaaat ggcacgttta ggtggtgaga ggtggatgag      360
gaaacaggca ccagtgcagc tgatttgacc tccagtggga tagatacgat tagcaccagg      420
atcgtgtctc attttgaacc cagatctgaa cagaattaag acgaacgagc tttcacaatt      480
gcagcagatg aagatccatt ggtaaattga tcaggatttt tggcctaccc tccaaagaaa      540
aggagcggaa agaatgtcgg agcgggccgc ggatgacgtc aggggggagc cgcgcgcgcg      600
ggcggcggcg gcgggcggag cagcggccgc ggccgcccgg cagcagcagc agcagcagca      660
gcagcagcag ccgccgcctc cgcagcccca gcggcagcag caccgcgcac cgcgcgccag      720
gcgcacacgg ccggaggagc gcgggcccgg gcgcgcctcc acctcggccg ccgcaatggc      780
gacggtcggg gagcgcaggc ctctgcccag tctgaagtg atgctgggac agtcgtggaa      840
tctgtgggtt gaggtctcca aacttctctg gaaggacggg acagaattgg acgaaagtgt      900
caaggagtgt gggaaaaacc gcgaagtcac ggggctctgt cggaagaca tgccaatatt      960
tggtttctgt ccagcccatg atgatttcta cttggtggtg tgtaacgact gtaatcaggt     1020
tgtcaaaccc caggcatctc aatcacatta tgaaagaaga catagctcat ccagcaagcc     1080
  
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|                                                                    |      |
|--------------------------------------------------------------------|------|
| gcctttggcc gttcctccca cttcagtatt ttctttcttc ccttctctgt ccaaaagcaa  | 1140 |
| aggaggcagt gcaagtggaa gcaaccgttc ttccagtga ggtgttctta gcgcacctc    | 1200 |
| atcaagttcc aagttgttga aatcacccaa agagaaactg cagctcagg ggaacaccag   | 1260 |
| gccaatgcat cccattcagc aaagtagagt tccccatggt agaatcatga caccctctgt  | 1320 |
| gaaagtggaa aagattcctc cgaaaatgga tggcacacta ctgaaatctg cggtagggcc  | 1380 |
| aacctgtcct gctactgtga gttccttagt caagcctggc cttaactgcc cctcaatacc  | 1440 |
| aaagccaacc ttgccttcac ctggacagat tctgaatggc aaagggttc ctgcaccgcc   | 1500 |
| cactctggaa aagaaacctg aagacaattc caataatagg aaatttttaa ataagagatt  | 1560 |
| atcagaaaga gagttagtc ctgacatcca ctgtggggtt attgatctcg acaccaagaa   | 1620 |
| gccccgcacc cggctcttga catgcaagac acattcctta acccagcgca gggctgtcca  | 1680 |
| gggtagaaga aaacgatttg atgtgttatt agccgagcac aaaaacaaaa ccagggaaaa  | 1740 |
| ggaattgatt cgccatccgg actctcagca accaccgcag cctctcaggg acccgcatcc  | 1800 |
| cgccctcctc agaacgtcac aggagccgca ccaaaacctc cacggagtga ttctctccga  | 1860 |
| atcaaagcct tttgtagcta gtaaacctaa acctcacacc ccaggtcttc caaggcctcc  | 1920 |
| aggctgccct gctcagcaag gtgggagtcg cccattgac cctctccag tccatgaatc    | 1980 |
| ttcacacctc cccctgcctg ccaactgagc agcttctcgg ttatccagtg aggagggcga  | 2040 |
| aggcgatgac aaagaagagt ctgttgaaaa actggactgt cattattcag gtcacatcc   | 2100 |
| tcagccagca tctttttgca catttgggag ccggcagata ggaagaggct attacgtgtt  | 2160 |
| tgactccagg tggaatcgac ttcgctgcgc cctcaacctc atggtggaga agcatctgaa  | 2220 |
| tgacagcta tggaagaaaa tcccaccagt gccagtagc acctcaccca tctccacag     | 2280 |
| tattctctac cggacaaact ctgtgcccgc atcacaaatgt ggagtcagct atctggcagc | 2340 |
| agccaccgtc tctacatccc cagtcctgct ctcatctacc tgcacatccc caaatagcaa  | 2400 |
| atcggtacca gctcatggaa ccacactaaa tgcacagcct gctgcttcag gggcgatgga  | 2460 |
| tcctgtgtgc agtatgcaat ccagacaagt gtctcttcca tctcatccc cttccacgcc   | 2520 |
| ctctggcctt tcctcgggtc cttctctccc catgtccagg aaacctcaga aattgaaatc  | 2580 |
| cagcaaatct ttgagccca aggagtcttc tggtaacagc actaactgtc aaaatgccag   | 2640 |
| tagcagtacc agtggcggtc caggaaagaa acgcaaaaac agttccccac tgttggttca  | 2700 |
| ctcttctccc tcctcttccc cctctctccc ttcttctcat tccatggagt cttttaggaa  | 2760 |
| aaactgtgtg gctcactctg ggcctcccta cccctcaacg gtaacatctt cccatagcat  | 2820 |
| cggcctcaac tgtgtgacga ataaagcaaa tgcgggtgaac gtcgggcatg accagtcagg | 2880 |
| gaggggcccc cccaccggga gccctgctga atccatcaag aggatgagtg tgatggtgaa  | 2940 |
| cagcagtgat tctactcttt ctcttgggcc attcattcac cagtccaatg aactgcctgt  | 3000 |
| caactccac ggcagttttt cccactcaca cactcctcta gacaaactca taggaaagaa   | 3060 |
| aagaaagtgc tcaccagct cgagcagcat caacaacagc agcagcaaac ccacaaaggt   | 3120 |
| tgccaaagtg ccagccgtga acaatgtcca catgaaacac acaggcacca tcccaggggc  | 3180 |
| acaaggactg atgaacagtt cctctcttca tcagccaaag gcacgtccct gacagctgaa  | 3240 |
| aatagcacgg ggaggaataa tgcggacact tttgaggaca agttacacct ccactcagca  | 3300 |
| ctctggactc cagtagcct ttgagtctgt tttcccaacc tcctgtgggc ctcaagggta   | 3360 |
| gaaacctgcc gggctgttgt tttaacgagg atttccctga agctatgtct ctagcagtga  | 3420 |
| gtactcataa aggacactgg atcaagttca gccaccgaat tgcttttatc agtggttaaag | 3480 |

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tggtctgaac tgcttgetac caatctgtga gaagtttttg tttttgtttt gttttttaac 3540
ttgcagtata tcacagagcc actcttcaag tagattggct gggcaaaaga atgttttggc 3600
aagagcggtta ctgtagacct ttctcctccc ttctttttac taccattttt ttttaacact 3660
gtcatctgta ggtcactctc cagcagtttag gcaccttaac tggagaccag aaaccttcca 3720
gagaacacag ggctgcatcc cgagcaaccc tctgaagaag ggaattaggc tttagatttt 3780
gatagcaatg ttccaggaat gaaatataga tgtagccca agacaccatg acaaaaatagc 3840
ccagcctttt gagagtaatt tgggaaaaga agctgtcaga agtttctaac ttacaaactg 3900
gtttgaaatt tttgatgccc agacagcaag tataaatcat tttggaggct tacttttcat 3960
gatacaaaag caattctgtg tgattttttt ttttaagaag aaagaaaatg caagctagtt 4020
ttgagaaagg aaggccaat tgggtcgggg gagggtgagg gtgaggaagt taaaatcact 4080
atagggagaa aaaacttttt tcaagatttc caaagagatg aaattttctt aatcctttta 4140
agttttcata gtaaacagta tggcagattg ggttggttgt cctacctggt ctatttttaa 4200
aagtacactt ttaaagtac attattagat aacttaaat gtttccaagg cactctctac 4260
attacccttg tttttctctt tggatactgt cctgggacta agtgtagatt tctgcttcaa 4320
gcacttctgg cattgtgtgt ttttgtatgc actccccttc atgccacttc agatgtttat 4380
ttggatgtgg ttggggacga gagcagacac caagga 4416

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&lt;210&gt; SEQ ID NO 49

&lt;211&gt; LENGTH: 892

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Homo Sapiens

&lt;400&gt; SEQUENCE: 49

```

Met Ser Glu Arg Ala Ala Asp Asp Val Arg Gly Glu Pro Arg Arg Ala
1      5      10      15
Ala Ala Ala Ala Gly Gly Ala Ala Ala Ala Ala Arg Gln Gln Gln
20     25     30
Gln Gln Gln Gln Gln Gln Gln Pro Pro Pro Gln Pro Gln Arg Gln
35     40     45
Gln His Pro Pro Pro Pro Arg Arg Thr Arg Pro Glu Asp Gly Gly
50     55     60
Pro Gly Ala Ala Ser Thr Ser Ala Ala Ala Met Ala Thr Val Gly Glu
65     70     75     80
Arg Arg Pro Leu Pro Ser Pro Glu Val Met Leu Gly Gln Ser Trp Asn
85     90     95
Leu Trp Val Glu Ala Ser Lys Leu Pro Gly Lys Asp Gly Thr Glu Leu
100    105    110
Asp Glu Ser Phe Lys Glu Phe Gly Lys Asn Arg Glu Val Met Gly Leu
115    120    125
Cys Arg Glu Asp Met Pro Ile Phe Gly Phe Cys Pro Ala His Asp Asp
130    135    140
Phe Tyr Leu Val Val Cys Asn Asp Cys Asn Gln Val Val Lys Pro Gln
145    150    155    160
Ala Phe Gln Ser His Tyr Glu Arg Arg His Ser Ser Ser Ser Lys Pro
165    170    175
Pro Leu Ala Val Pro Pro Thr Ser Val Phe Ser Phe Phe Pro Ser Leu
180    185    190
Ser Lys Ser Lys Gly Gly Ser Ala Ser Gly Ser Asn Arg Ser Ser Ser
195    200    205

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|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Gly | Val | Leu | Ser | Ala | Ser | Ser | Ser | Ser | Ser | Lys | Leu | Leu | Lys | Ser |
| 210 |     |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |
| Pro | Lys | Glu | Lys | Leu | Gln | Leu | Arg | Gly | Asn | Thr | Arg | Pro | Met | His | Pro |
| 225 |     |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |
| Ile | Gln | Gln | Ser | Arg | Val | Pro | His | Gly | Arg | Ile | Met | Thr | Pro | Ser | Val |
|     |     |     |     | 245 |     |     |     |     | 250 |     |     |     |     | 255 |     |
| Lys | Val | Glu | Lys | Ile | His | Pro | Lys | Met | Asp | Gly | Thr | Leu | Leu | Lys | Ser |
|     |     |     | 260 |     |     |     |     | 265 |     |     |     |     | 270 |     |     |
| Ala | Val | Gly | Pro | Thr | Cys | Pro | Ala | Thr | Val | Ser | Ser | Leu | Val | Lys | Pro |
|     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |
| Gly | Leu | Asn | Cys | Pro | Ser | Ile | Pro | Lys | Pro | Thr | Leu | Pro | Ser | Pro | Gly |
|     | 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |
| Gln | Ile | Leu | Asn | Gly | Lys | Gly | Leu | Pro | Ala | Pro | Pro | Thr | Leu | Glu | Lys |
| 305 |     |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |
| Lys | Pro | Glu | Asp | Asn | Ser | Asn | Asn | Arg | Lys | Phe | Leu | Asn | Lys | Arg | Leu |
|     |     |     |     | 325 |     |     |     |     | 330 |     |     |     |     | 335 |     |
| Ser | Glu | Arg | Glu | Phe | Asp | Pro | Asp | Ile | His | Cys | Gly | Val | Ile | Asp | Leu |
|     |     |     | 340 |     |     |     |     | 345 |     |     |     |     | 350 |     |     |
| Asp | Thr | Lys | Lys | Pro | Cys | Thr | Arg | Ser | Leu | Thr | Cys | Lys | Thr | His | Ser |
|     |     | 355 |     |     |     |     | 360 |     |     |     |     | 365 |     |     |     |
| Leu | Thr | Gln | Arg | Arg | Ala | Val | Gln | Gly | Arg | Arg | Lys | Arg | Phe | Asp | Val |
|     | 370 |     |     |     |     | 375 |     |     |     |     | 380 |     |     |     |     |
| Leu | Leu | Ala | Glu | His | Lys | Asn | Lys | Thr | Arg | Glu | Lys | Glu | Leu | Ile | Arg |
| 385 |     |     |     |     | 390 |     |     |     |     | 395 |     |     |     |     | 400 |
| His | Pro | Asp | Ser | Gln | Gln | Pro | Pro | Gln | Pro | Leu | Arg | Asp | Pro | His | Pro |
|     |     |     |     | 405 |     |     |     |     | 410 |     |     |     |     | 415 |     |
| Ala | Pro | Pro | Arg | Thr | Ser | Gln | Glu | Pro | His | Gln | Asn | Pro | His | Gly | Val |
|     |     |     | 420 |     |     |     |     | 425 |     |     |     |     | 430 |     |     |
| Ile | Pro | Ser | Glu | Ser | Lys | Pro | Phe | Val | Ala | Ser | Lys | Pro | Lys | Pro | His |
|     |     | 435 |     |     |     |     | 440 |     |     |     |     | 445 |     |     |     |
| Thr | Pro | Ser | Leu | Pro | Arg | Pro | Pro | Gly | Cys | Pro | Ala | Gln | Gln | Gly | Gly |
|     | 450 |     |     |     |     | 455 |     |     |     |     | 460 |     |     |     |     |
| Ser | Ala | Pro | Ile | Asp | Pro | Pro | Pro | Val | His | Glu | Ser | Pro | His | Pro | Pro |
| 465 |     |     |     |     | 470 |     |     |     |     | 475 |     |     |     |     | 480 |
| Leu | Pro | Ala | Thr | Glu | Pro | Ala | Ser | Arg | Leu | Ser | Ser | Glu | Glu | Gly | Glu |
|     |     |     |     | 485 |     |     |     |     | 490 |     |     |     |     | 495 |     |
| Gly | Asp | Asp | Lys | Glu | Glu | Ser | Val | Glu | Lys | Leu | Asp | Cys | His | Tyr | Ser |
|     |     |     | 500 |     |     |     |     | 505 |     |     |     | 510 |     |     |     |
| Gly | His | His | Pro | Gln | Pro | Ala | Ser | Phe | Cys | Thr | Phe | Gly | Ser | Arg | Gln |
|     |     | 515 |     |     |     |     | 520 |     |     |     |     | 525 |     |     |     |
| Ile | Gly | Arg | Gly | Tyr | Tyr | Val | Phe | Asp | Ser | Arg | Trp | Asn | Arg | Leu | Arg |
|     | 530 |     |     |     |     | 535 |     |     |     |     | 540 |     |     |     |     |
| Cys | Ala | Leu | Asn | Leu | Met | Val | Glu | Lys | His | Leu | Asn | Ala | Gln | Leu | Trp |
| 545 |     |     |     |     | 550 |     |     |     |     | 555 |     |     |     |     | 560 |
| Lys | Lys | Ile | Pro | Pro | Val | Pro | Ser | Thr | Thr | Ser | Pro | Ile | Ser | Thr | Arg |
|     |     |     |     | 565 |     |     |     |     | 570 |     |     |     |     | 575 |     |
| Ile | Pro | His | Arg | Thr | Asn | Ser | Val | Pro | Thr | Ser | Gln | Cys | Gly | Val | Ser |
|     |     |     | 580 |     |     |     |     | 585 |     |     |     |     | 590 |     |     |
| Tyr | Leu | Ala | Ala | Ala | Thr | Val | Ser | Thr | Ser | Pro | Val | Leu | Leu | Ser | Ser |
|     |     | 595 |     |     |     |     | 600 |     |     |     |     | 605 |     |     |     |
| Thr | Cys | Ile | Ser | Pro | Asn | Ser | Lys | Ser | Val | Pro | Ala | His | Gly | Thr | Thr |
|     | 610 |     |     |     |     | 615 |     |     |     |     | 620 |     |     |     |     |
| Leu | Asn | Ala | Gln | Pro | Ala | Ala | Ser | Gly | Ala | Met | Asp | Pro | Val | Cys | Ser |
| 625 |     |     |     |     | 630 |     |     |     |     | 635 |     |     |     |     | 640 |

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Met Gln Ser Arg Gln Val Ser Ser Ser Ser Ser Ser Pro Ser Thr Pro  
645 650 655

Ser Gly Leu Ser Ser Val Pro Ser Ser Pro Met Ser Arg Lys Pro Gln  
660 665 670

Lys Leu Lys Ser Ser Lys Ser Leu Arg Pro Lys Glu Ser Ser Gly Asn  
675 680 685

Ser Thr Asn Cys Gln Asn Ala Ser Ser Ser Thr Ser Gly Gly Ser Gly  
690 695 700

Lys Lys Arg Lys Asn Ser Ser Pro Leu Leu Val His Ser Ser Ser Ser  
705 710 715 720

Ser Ser Ser Ser Ser Ser Ser Ser His Ser Met Glu Ser Phe Arg Lys  
725 730 735

Asn Cys Val Ala His Ser Gly Pro Pro Tyr Pro Ser Thr Val Thr Ser  
740 745 750

Ser His Ser Ile Gly Leu Asn Cys Val Thr Asn Lys Ala Asn Ala Val  
755 760 765

Asn Val Arg His Asp Gln Ser Gly Arg Gly Pro Pro Thr Gly Ser Pro  
770 775 780

Ala Glu Ser Ile Lys Arg Met Ser Val Met Val Asn Ser Ser Asp Ser  
785 790 795 800

Thr Leu Ser Leu Gly Pro Phe Ile His Gln Ser Asn Glu Leu Pro Val  
805 810 815

Asn Ser His Gly Ser Phe Ser His Ser His Thr Pro Leu Asp Lys Leu  
820 825 830

Ile Gly Lys Lys Arg Lys Cys Ser Pro Ser Ser Ser Ser Ile Asn Asn  
835 840 845

Ser Ser Ser Lys Pro Thr Lys Val Ala Lys Val Pro Ala Val Asn Asn  
850 855 860

Val His Met Lys His Thr Gly Thr Ile Pro Gly Ala Gln Gly Leu Met  
865 870 875 880

Asn Ser Ser Leu Leu His Gln Pro Lys Ala Arg Pro  
885 890

&lt;210&gt; SEQ ID NO 50

&lt;211&gt; LENGTH: 1867

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Homo Sapiens

&lt;400&gt; SEQUENCE: 50

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ggttcgctgt ggcgggcgcc tgggcccgcg gctgtttaac ttcgcttcg ctggcccata    60
gtgatctttg cagtgaacca gcagcatcac tgtttcttgg cgtgtgaaga taaccaagg    120
aattgaggaa gttgctgaga agagtgtgct ggagatgctc taggaaaaaa ttgaatagtg    180
agacgagttc cagcgcaagg gtttctggtt tgccaagaag aaagtgaaca tcatggatca    240
gaacaacagc ctgccacctt acgctcaggg cttggcctcc cctcaggggtg ccatgactcc    300
cggaatccct atctttatgc caatgatgcc ttatggcact ggactgaccc cacagcctat    360
tcagaacacc aatagtctgt ctattttggg agagcaacaa aggagcagc agcaacaaca    420
acagcagcag cagcagcagc agcagcaaca gcaacagcag cagcagcagc agcagcagca    480
gcagcagcag cagcagcagc agcagcagca gcaacaggca gtggcagctg cagccgttca    540
gcagtcaacg tcccagcagg caacacaggg aacctcaggc caggcaccac agctcttcca    600
ctcacagact ctcacaactg cacccttgcc gggcaccact ccaactgtatc cctcccccat    660
gactcccatg acccccatac ctctgccac gccagcttcg gagagttctg ggattgtacc    720

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cgagctgcaa aatattgtat ccacagtga tcttggttgt aaacttgacc taaagaccat 780
tgcacttcgt gcccgaacg ccgaatataa tccaagcgg tttgctgcgg taatcatgag 840
gataagagag ccacgaacca cggcactgat tttcagttct gggaaaatgg tgtgcacagg 900
agccaagagt gaagaacagt ccagactggc agcaagaaaa tatgctagag ttgtacagaa 960
gttgggtttt ccagctaagt tcttggaact caagattcag aatatgggtg ggagctgtga 1020
tgtgaagttt cctataaggt tagaaggcct tgtgtcacc caccaacaat ttagtagtta 1080
tgagccagag ttatttcctg gtttaactca cagaatgatc aaaccagaa ttgttctcct 1140
tatttttgtt tctgaaaag ttgtattaac aggtgctaaa gtcagagcag aaatttatga 1200
agcatttgaa aacatctacc ctattctaaa gggattcagg aagacgacgt aatggctctc 1260
atgtaccctt gcctccccc ccccttctt ttttttttt taaacaaatc agtttgtttt 1320
ggtaaccttta aatgggtggtg ttgtgagaag atggatgttg agttgcaggg tgtggcacca 1380
ggtgatgccc ttctgtaagt gcccaccgcg ggatgccggg aaggggcatt atttgtgcac 1440
tgagaacacc gcgcagcgtg actgtgagtt gctcatacgg tgctgctatc tgggcagcgc 1500
tgcccattta ttatatgta gattttaaac actgctgttg acaagttggt ttgagggaga 1560
aaactttaag tgtaaaaggc acctctataa ttgattggac tttttaattt taatgttttt 1620
ccccatgaac cacagttttt atatttctac cagaaaagta aaaatctttt taaaagtgt 1680
tgtttttcta atttataact ctaggggtt atttctgtgc cagacacatt ccacctctcc 1740
agtattgcag gacagaatat atgtgttaat gaaaatgaat ggctgtacat atttttttct 1800
ttcttcagag tactctgtac aataaatgca gtttataaaa gtgttaaaaa aaaaaaaaaa 1860
aaaaaaa 1867

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&lt;210&gt; SEQ ID NO 51

&lt;211&gt; LENGTH: 344

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Homo Sapiens

&lt;400&gt; SEQUENCE: 51

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Met Asp Gln Asn Asn Ser Leu Pro Pro Tyr Ala Gln Gly Leu Ala Ser
1          5          10          15

Pro Gln Gly Ala Met Thr Pro Gly Ile Pro Ile Phe Ser Pro Met Met
20          25          30

Pro Tyr Gly Thr Gly Leu Thr Pro Gln Pro Ile Gln Asn Thr Asn Ser
35          40          45

Leu Ser Ile Leu Glu Glu Gln Gln Arg Gln Gln Gln Gln Gln Gln
50          55          60

Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln
65          70          75          80

Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Ala
85          90          95

Val Ala Ala Ala Ala Val Gln Gln Ser Thr Ser Gln Gln Ala Thr Gln
100         105         110

Gly Thr Ser Gly Gln Ala Pro Gln Leu Phe His Ser Gln Thr Leu Thr
115         120         125

Thr Ala Pro Leu Pro Gly Thr Thr Pro Leu Tyr Pro Ser Pro Met Thr
130         135         140

Pro Met Thr Pro Ile Thr Pro Ala Thr Pro Ala Ser Glu Ser Ser Gly
145         150         155         160

Ile Val Pro Gln Leu Gln Asn Ile Val Ser Thr Val Asn Leu Gly Cys

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| 165 |     |     |     |     | 170 |     |     |     |     | 175 |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Lys | Leu | Asp | Leu | Lys | Thr | Ile | Ala | Leu | Arg | Ala | Arg | Asn | Ala | Glu | Tyr |
|     |     |     | 180 |     |     |     |     |     | 185 |     |     |     | 190 |     |     |
| Asn | Pro | Lys | Arg | Phe | Ala | Ala | Val | Ile | Met | Arg | Ile | Arg | Glu | Pro | Arg |
|     |     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |
| Thr | Thr | Ala | Leu | Ile | Phe | Ser | Ser | Gly | Lys | Met | Val | Cys | Thr | Gly | Ala |
|     |     | 210 |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |
| Lys | Ser | Glu | Glu | Gln | Ser | Arg | Leu | Ala | Ala | Arg | Lys | Tyr | Ala | Arg | Val |
|     |     | 225 |     |     |     |     | 230 |     |     |     |     | 235 |     |     | 240 |
| Val | Gln | Lys | Leu | Gly | Phe | Pro | Ala | Lys | Phe | Leu | Asp | Phe | Lys | Ile | Gln |
|     |     |     | 245 |     |     |     |     |     | 250 |     |     |     |     | 255 |     |
| Asn | Met | Val | Gly | Ser | Cys | Asp | Val | Lys | Phe | Pro | Ile | Arg | Leu | Glu | Gly |
|     |     |     | 260 |     |     |     |     |     | 265 |     |     |     |     | 270 |     |
| Leu | Val | Leu | Thr | His | Gln | Gln | Phe | Ser | Ser | Tyr | Glu | Pro | Glu | Leu | Phe |
|     |     |     | 275 |     |     |     |     |     | 280 |     |     |     |     | 285 |     |
| Pro | Gly | Leu | Ile | Tyr | Arg | Met | Ile | Lys | Pro | Arg | Ile | Val | Leu | Leu | Ile |
|     |     | 290 |     |     |     |     |     |     | 295 |     |     |     |     | 300 |     |
| Phe | Val | Ser | Gly | Lys | Val | Val | Leu | Thr | Gly | Ala | Lys | Val | Arg | Ala | Glu |
|     |     | 305 |     |     |     |     |     |     | 310 |     |     |     |     | 315 | 320 |
| Ile | Tyr | Glu | Ala | Phe | Glu | Asn | Ile | Tyr | Pro | Ile | Leu | Lys | Gly | Phe | Arg |
|     |     |     | 325 |     |     |     |     |     | 330 |     |     |     |     | 335 |     |
| Lys | Thr | Thr | Asp | Arg | Asx | Pro | Leu |     |     |     |     |     |     |     |     |
|     |     |     | 340 |     |     |     |     |     |     |     |     |     |     |     |     |

&lt;210&gt; SEQ ID NO 52

&lt;211&gt; LENGTH: 4367

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Homo Sapiens

&lt;400&gt; SEQUENCE: 52

|                                                                    |      |
|--------------------------------------------------------------------|------|
| gacgccatac tggagccaa gtgggaggaa cttcaaggct gtccctcgcg ggcctcccg    | 60   |
| tctgcttctg cgaaggttct attgaaaaca gatcctgcaa aagttccagg tgccacact   | 120  |
| ggaaacttgg agatcctgct tcccagacca cagctgtggg gaacttgggg tggagcagag  | 180  |
| aagtttctgt attcagctgc ccaggcagag gagaatgggg tctccacagc ctgaagaatg  | 240  |
| aagacacgac agaataaaga ctcgatgtca atgaggagtg gacggaagaa agaggcccct  | 300  |
| gggccccggg aagaactgag atcgaggggc cgggcctccc ctggaggggt cagcacgtcc  | 360  |
| agcagtgatg gcaaagctga gaagtccagg cagacagcca agaaggcccg agtagaggaa  | 420  |
| gcctccaccc caaaggtcaa caagcagggt cggagtgagg agatctcaga gagtgaaggt  | 480  |
| gaggagacca atgcacaaa aaagacaaa actgagcagg aactccctcg gccacagtct    | 540  |
| ccctccgatac tggatagctt ggacgggcgg agccttaatg atgatggcag cagcgaccct | 600  |
| agggatatcg accaggacaa ccgaagcacg tccccagta tctacagccc tggaagtgtg   | 660  |
| gagaatgact ctgactcatt ttctggcctg tcccagggcc cagcccggcc ctaccaccca  | 720  |
| cctccactct ttctccttc ccctcaaccg ccagacagca cccctcgaca gccagaggct   | 780  |
| agctttgaac cccatccttc tgtgacaccc actggatata atgctcccat ggagccccc   | 840  |
| acatctcgaa tgttccaggc tctctctggg gccctcccc ctcaccacaca gctctatcct  | 900  |
| gggggcactg gtggagtttt gtctggaccc ccaatgggtc ccaagggggg aggggctgcc  | 960  |
| tcatcagtgg ggggcccata tgggggtaag cagcaccccc caccactac tcccatttca   | 1020 |
| gtatcaagct ctggggctag tgggtctccc ccaacaaagc cgcctaccac tccagtgggt  | 1080 |
| ggtgggaacc taccttctgc tccaccacca gccaaacttc cccatgtgac accgaacctg  | 1140 |

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|            |            |            |            |             |            |      |
|------------|------------|------------|------------|-------------|------------|------|
| cctccccac  | ctgccctgag | acccctcaac | aatgcacag  | cctctcccc   | tggectggg  | 1200 |
| gcccaccac  | tacctggtca | tctgacctct | ccccacgcca | tgggacagg   | tatgggtgga | 1260 |
| cttctctctg | gcccagagaa | gggcccaact | ctggctcctt | cacccactc   | tctgctcct  | 1320 |
| gcttctctct | ctgctccage | gcccccatg  | aggtttctt  | attcatctc   | tagtagtagc | 1380 |
| tctgcagcag | cctcctcttc | cagttcttcc | tcctcttct  | ctgctcccc   | cttccagct  | 1440 |
| tcccaggcat | tgcccageta | ccccactct  | ttccctcccc | caacaagcct  | ctctgtctcc | 1500 |
| aatcagcccc | ccaagtatac | tcagccttct | ctcccatccc | aggctgtgtg  | gagccagggt | 1560 |
| ccccaccac  | ctcctcccta | tggccgctc  | ttagccaaca | gcaatgccc   | tccaggcccc | 1620 |
| ttccctccct | ctactggggc | ccagtcaccc | gcccaccac  | cagtctcaac  | acatcaccat | 1680 |
| caccaccagc | aacagcaaca | gcagcagcag | cagcagcagc | agcagcagca  | gcagcagcag | 1740 |
| cagcatcacg | gaaactctgg | gccccctct  | cctggagcat | ttccccccc   | actggagggc | 1800 |
| ggtagctccc | accacgcaca | cccttacgcc | atgtctccct | ccctggggtc  | tctgaggccc | 1860 |
| taccaccag  | ggccagcaca | cctgccccca | cctcacagcc | agggtgtcta  | cagccaagca | 1920 |
| ggccccaatg | gcctccagct | ctcttctct  | tccaactctt | cctcttcac   | ttctcaagg  | 1980 |
| tctaccctat | gttcacaccc | ctcccccttc | cagggccctc | aagggcgcc   | ctaccctttc | 2040 |
| ccaccggtgc | ctacggtcac | cacctcttcg | gtacccttt  | ccacggctcat | tgccaccgtg | 2100 |
| gcttctctcg | cagcaggcta | caaaacggcc | tccccacctg | ggccccacc   | gtacggaaag | 2160 |
| agagcccgct | ccccgggggc | ctacaagaca | gccacccac  | cgggatacaa  | acccgggtcg | 2220 |
| cctccctct  | tccgaacggg | gacccaccg  | ggctatcgag | gaacctcgcc  | acctgcaggc | 2280 |
| ccagggacct | tcaagccggg | ctcgccacc  | gtgggacctg | ggccctgcc   | acctgcgggg | 2340 |
| ccctcaggcc | tgccatcgct | gccaccacca | cctgcggccc | ctgctcagg   | gccgccctg  | 2400 |
| agcgccacgc | agatcaaaca | ggagccggct | gaggagtatg | agacccccga  | gagcccggtg | 2460 |
| ccccagccc  | gcagccctc  | gccccctccc | aaggtggtag | atgtaccag   | ccatgccagt | 2520 |
| cagtctgcca | ggttcaacaa | acacctggat | cgcggcttca | actcgtcgc   | gcgcagcgac | 2580 |
| ctgtacttcg | tgccactgga | gggctccaag | ctggccaaga | agcgggccga  | cctggtggag | 2640 |
| aagggtcgcc | gcgagccga  | gcagcgcgcg | cgcgaagaaa | aggagcgcca  | gcgcgagcgg | 2700 |
| gaacgcgaga | aagagcgcca | gcgcgagaag | gagcgcgagc | ttgaacgcag  | cgtgaagtgt | 2760 |
| gctcaggagg | gccgtgctcc | ggtggaatgc | ccatctctgg | gccagtgcc   | ccatcgccct | 2820 |
| ccatttgaac | cgggcagtg  | ggtggctaca | gtgccccct  | acctgggtcc  | tgacactcca | 2880 |
| gccttgcgca | ctctcagtga | atatgcccgg | cctcatgtca | tgtctcttg   | caatcgcaac | 2940 |
| catccattct | acgtgcccct | gggggcagtg | gacccggggc | tcctgggtta  | caatgtccc  | 3000 |
| gccctgtaca | gcagtgatcc | agctgcccgg | gagagggaac | gggaagccc   | tgaacgagac | 3060 |
| ctccgtgacc | gcctcaagcc | tggttttgag | gtgaagccta | gtgagctgga  | acccctacat | 3120 |
| gggtccctg  | ggccgggctt | ggatcccttt | ccccgacatg | ggggcctggc  | tctgcagcct | 3180 |
| ggccacctg  | gcctgcaccc | tttcccttt  | catccgagcc | tggggccct   | ggagcgagaa | 3240 |
| cgtctagcgc | tggcagctgg | gccagccctg | cggcctgaca | tgtcctatgc  | tgagcggtg  | 3300 |
| gcagctgaga | ggcagcacgc | agaaagggtg | gcggccctgg | gcaatgaccc  | actggcccgg | 3360 |
| ctgcagatgc | tcaatgtgac | ttcccatcac | caccagcact | cccacatcca  | ctcgcacctg | 3420 |
| cacctgcacc | agcaagatgc | tatccatgca | gcctctgcct | cgggtgcacc  | tctcattgac | 3480 |
| ccccggcct  | cagggtctca | ccttaaccgg | atccctacc  | cagctggaac  | tctccctaac | 3540 |

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ccccgtcttc ctcacctctc gcacgagaac gaagttcttc gtcaccagct ctttgtctgcc 3600
ccttacccggg acctgcgcgc ctccctttct gcccgcgatgt cagcagctca tcagctgcag 3660
gccatgcacg cacagtcacg tgagctgcag cgcttgccgc tggaacagca gcagtggctg 3720
catgcccac acccgctgca cagtgtgccg ctgcctgccc aggaggacta ctacagtcac 3780
ctgaagaagg aaagcgacaa gccactgtag aacctgcgat caagagagca ccatggctcc 3840
tacattggac cttggagcac ccccacctc ccccaccgt gcccttgcc tgcacccag 3900
agccaagagg gtgctgctca gttgcagggc ctccgcagct ggacagagag tgggggaggg 3960
agggacagac agaaggccaa ggcccgatgt ggtgtgcaga ggtggggagg tggcgaggat 4020
ggggacagaa agcgcacaga atcttgacc aggtctctct tccttgctcc cctgctttt 4080
ctctccccc atgcccacc cctgtggccg ccgcccctcc cctgcccgt tggtgtgatt 4140
atttcactg ttagatgtgg ctgttttgcg tagcatcgtg tgccaccct gccctcccc 4200
gatccctgtg tgcgcgcccc ctctgcaatg tatgcccctt gccccttccc cacactaata 4260
atttatatat ataatatctc atatgacgct cttaaaaaaa catcccaacc aaaaccaacc 4320
aaacaaaaac atcctcacia ctcccagga aaaaaaaaaa aaaaaaa 4367

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&lt;210&gt; SEQ ID NO 53

&lt;211&gt; LENGTH: 1194

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Homo Sapiens

&lt;400&gt; SEQUENCE: 53

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Met Lys Thr Arg Gln Asn Lys Asp Ser Met Ser Met Arg Ser Gly Arg
1           5           10           15
Lys Lys Glu Ala Pro Gly Pro Arg Glu Glu Leu Arg Ser Arg Gly Arg
20          25          30
Ala Ser Pro Gly Gly Val Ser Thr Ser Ser Ser Asp Gly Lys Ala Glu
35          40          45
Lys Ser Arg Gln Thr Ala Lys Lys Ala Arg Val Glu Glu Ala Ser Thr
50          55          60
Pro Lys Val Asn Lys Gln Gly Arg Ser Glu Glu Ile Ser Glu Ser Glu
65          70          75          80
Ser Glu Glu Thr Asn Ala Pro Lys Lys Thr Lys Thr Glu Gln Glu Leu
85          90          95
Pro Arg Pro Gln Ser Pro Ser Asp Leu Asp Ser Leu Asp Gly Arg Ser
100         105         110
Leu Asn Asp Asp Gly Ser Ser Asp Pro Arg Asp Ile Asp Gln Asp Asn
115         120         125
Arg Ser Thr Ser Pro Ser Ile Tyr Ser Pro Gly Ser Val Glu Asn Asp
130         135         140
Ser Asp Ser Ser Ser Gly Leu Ser Gln Gly Pro Ala Arg Pro Tyr His
145         150         155         160
Pro Pro Pro Leu Phe Pro Pro Ser Pro Gln Pro Pro Asp Ser Thr Pro
165         170         175
Arg Gln Pro Glu Ala Ser Phe Glu Pro His Pro Ser Val Thr Pro Thr
180         185         190
Gly Tyr His Ala Pro Met Glu Pro Pro Thr Ser Arg Met Phe Gln Ala
195         200         205
Pro Pro Gly Ala Pro Pro Pro His Pro Gln Leu Tyr Pro Gly Gly Thr
210         215         220
Gly Gly Val Leu Ser Gly Pro Pro Met Gly Pro Lys Gly Gly Gly Ala

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| 225                                                             | 230 | 235 | 240 |
|-----------------------------------------------------------------|-----|-----|-----|
| Ala Ser Ser Val Gly Gly Pro Asn Gly Gly Lys Gln His Pro Pro Pro | 245 | 250 | 255 |
| Thr Thr Pro Ile Ser Val Ser Ser Ser Gly Ala Ser Gly Ala Pro Pro | 260 | 265 | 270 |
| Thr Lys Pro Pro Thr Thr Pro Val Gly Gly Gly Asn Leu Pro Ser Ala | 275 | 280 | 285 |
| Pro Pro Pro Ala Asn Phe Pro His Val Thr Pro Asn Leu Pro Pro Pro | 290 | 295 | 300 |
| Pro Ala Leu Arg Pro Leu Asn Asn Ala Ser Ala Ser Pro Pro Gly Leu | 305 | 310 | 315 |
| Gly Ala Gln Pro Leu Pro Gly His Leu Pro Ser Pro His Ala Met Gly | 325 | 330 | 335 |
| Gln Gly Met Gly Gly Leu Pro Pro Gly Pro Glu Lys Gly Pro Thr Leu | 340 | 345 | 350 |
| Ala Pro Ser Pro His Ser Leu Pro Pro Ala Ser Ser Ser Ala Pro Ala | 355 | 360 | 365 |
| Pro Pro Met Arg Phe Pro Tyr Ser Ser Ser Ser Ser Ser Ala Ala     | 370 | 375 | 380 |
| Ala Ser Ser Ser Ser Ser Ser Ser Ser Ser Ala Ser Pro Phe Pro     | 385 | 390 | 395 |
| Ala Ser Gln Ala Leu Pro Ser Tyr Pro His Ser Phe Pro Pro Pro Thr | 405 | 410 | 415 |
| Ser Leu Ser Val Ser Asn Gln Pro Pro Lys Tyr Thr Gln Pro Ser Leu | 420 | 425 | 430 |
| Pro Ser Gln Ala Val Trp Ser Gln Gly Pro Pro Pro Pro Pro Tyr     | 435 | 440 | 445 |
| Gly Arg Leu Leu Ala Asn Ser Asn Ala His Pro Gly Pro Phe Pro Pro | 450 | 455 | 460 |
| Ser Thr Gly Ala Gln Ser Thr Ala His Pro Pro Val Ser Thr His His | 465 | 470 | 475 |
| His His His Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln     | 485 | 490 | 495 |
| Gln Gln Gln Gln Gln Gln His His Gly Asn Ser Gly Pro Pro Pro Pro | 500 | 505 | 510 |
| Gly Ala Phe Pro His Pro Leu Glu Gly Gly Ser Ser His His Ala His | 515 | 520 | 525 |
| Pro Tyr Ala Met Ser Pro Ser Leu Gly Ser Leu Arg Pro Tyr Pro Pro | 530 | 535 | 540 |
| Gly Pro Ala His Leu Pro Pro Pro His Ser Gln Val Ser Tyr Ser Gln | 545 | 550 | 555 |
| Ala Gly Pro Asn Gly Pro Pro Val Ser Ser Ser Ser Asn Ser Ser Ser | 565 | 570 | 575 |
| Ser Thr Ser Gln Gly Ser Tyr Pro Cys Ser His Pro Ser Pro Ser Gln | 580 | 585 | 590 |
| Gly Pro Gln Gly Ala Pro Tyr Pro Phe Pro Pro Val Pro Thr Val Thr | 595 | 600 | 605 |
| Thr Ser Ser Ala Thr Leu Ser Thr Val Ile Ala Thr Val Ala Ser Ser | 610 | 615 | 620 |
| Pro Ala Gly Tyr Lys Thr Ala Ser Pro Pro Gly Pro Pro Pro Tyr Gly | 625 | 630 | 635 |
| Lys Arg Ala Pro Ser Pro Gly Ala Tyr Lys Thr Ala Thr Pro Pro Gly | 645 | 650 | 655 |

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|     |      |     |     |     |     |      |     |     |     |     |     |      |     |     |     |  |
|-----|------|-----|-----|-----|-----|------|-----|-----|-----|-----|-----|------|-----|-----|-----|--|
| Tyr | Lys  | Pro | Gly | Ser | Pro | Pro  | Ser | Phe | Arg | Thr | Gly | Thr  | Pro | Pro | Gly |  |
|     |      |     | 660 |     |     |      |     | 665 |     |     |     |      | 670 |     |     |  |
| Tyr | Arg  | Gly | Thr | Ser | Pro | Pro  | Ala | Gly | Pro | Gly | Thr | Phe  | Lys | Pro | Gly |  |
|     |      | 675 |     |     |     |      | 680 |     |     |     |     | 685  |     |     |     |  |
| Ser | Pro  | Thr | Val | Gly | Pro | Gly  | Pro | Leu | Pro | Pro | Ala | Gly  | Pro | Ser | Gly |  |
|     |      | 690 |     |     |     | 695  |     |     |     |     | 700 |      |     |     |     |  |
| Leu | Pro  | Ser | Leu | Pro | Pro | Pro  | Pro | Ala | Ala | Pro | Ala | Ser  | Gly | Pro | Pro |  |
| 705 |      |     |     |     | 710 |      |     |     |     | 715 |     |      |     |     | 720 |  |
| Leu | Ser  | Ala | Thr | Gln | Ile | Lys  | Gln | Glu | Pro | Ala | Glu | Glu  | Tyr | Glu | Thr |  |
|     |      |     |     | 725 |     |      |     |     | 730 |     |     |      |     | 735 |     |  |
| Pro | Glu  | Ser | Pro | Val | Pro | Pro  | Ala | Arg | Ser | Pro | Ser | Pro  | Pro | Pro | Lys |  |
|     |      |     | 740 |     |     |      |     | 745 |     |     |     |      | 750 |     |     |  |
| Val | Val  | Asp | Val | Pro | Ser | His  | Ala | Ser | Gln | Ser | Ala | Arg  | Phe | Asn | Lys |  |
|     |      | 755 |     |     |     |      | 760 |     |     |     |     | 765  |     |     |     |  |
| His | Leu  | Asp | Arg | Gly | Phe | Asn  | Ser | Cys | Ala | Arg | Ser | Asp  | Leu | Tyr | Phe |  |
|     | 770  |     |     |     |     | 775  |     |     |     |     | 780 |      |     |     |     |  |
| Val | Pro  | Leu | Glu | Gly | Ser | Lys  | Leu | Ala | Lys | Lys | Arg | Ala  | Asp | Leu | Val |  |
| 785 |      |     |     |     | 790 |      |     |     |     | 795 |     |      |     |     | 800 |  |
| Glu | Lys  | Val | Arg | Arg | Glu | Ala  | Glu | Gln | Arg | Ala | Arg | Glu  | Glu | Lys | Glu |  |
|     |      |     |     | 805 |     |      |     |     | 810 |     |     |      |     | 815 |     |  |
| Arg | Glu  | Arg | Glu | Arg | Glu | Arg  | Glu | Lys | Glu | Arg | Glu | Arg  | Glu | Lys | Glu |  |
|     |      |     | 820 |     |     |      |     | 825 |     |     |     |      | 830 |     |     |  |
| Arg | Glu  | Leu | Glu | Arg | Ser | Val  | Lys | Leu | Ala | Gln | Glu | Gly  | Arg | Ala | Pro |  |
|     |      | 835 |     |     |     |      | 840 |     |     |     |     | 845  |     |     |     |  |
| Val | Glu  | Cys | Pro | Ser | Leu | Gly  | Pro | Val | Pro | His | Arg | Pro  | Pro | Phe | Glu |  |
|     | 850  |     |     |     |     | 855  |     |     |     |     | 860 |      |     |     |     |  |
| Pro | Gly  | Ser | Ala | Val | Ala | Thr  | Val | Pro | Pro | Tyr | Leu | Gly  | Pro | Asp | Thr |  |
| 865 |      |     |     |     | 870 |      |     |     |     | 875 |     |      |     |     | 880 |  |
| Pro | Ala  | Leu | Arg | Thr | Leu | Ser  | Glu | Tyr | Ala | Arg | Pro | His  | Val | Met | Ser |  |
|     |      |     |     | 885 |     |      |     |     | 890 |     |     |      |     | 895 |     |  |
| Pro | Gly  | Asn | Arg | Asn | His | Pro  | Phe | Tyr | Val | Pro | Leu | Gly  | Ala | Val | Asp |  |
|     |      | 900 |     |     |     |      | 905 |     |     |     |     |      | 910 |     |     |  |
| Pro | Gly  | Leu | Leu | Gly | Tyr | Asn  | Val | Pro | Ala | Leu | Tyr | Ser  | Ser | Asp | Pro |  |
|     |      | 915 |     |     |     | 920  |     |     |     |     |     | 925  |     |     |     |  |
| Ala | Ala  | Arg | Glu | Arg | Glu | Arg  | Glu | Ala | Arg | Glu | Arg | Asp  | Leu | Arg | Asp |  |
|     | 930  |     |     |     |     | 935  |     |     |     |     |     | 940  |     |     |     |  |
| Arg | Leu  | Lys | Pro | Gly | Phe | Glu  | Val | Lys | Pro | Ser | Glu | Leu  | Glu | Pro | Leu |  |
| 945 |      |     |     |     | 950 |      |     |     |     | 955 |     |      |     |     | 960 |  |
| His | Gly  | Val | Pro | Gly | Pro | Gly  | Leu | Asp | Pro | Phe | Pro | Arg  | His | Gly | Gly |  |
|     |      |     |     | 965 |     |      |     |     | 970 |     |     |      |     | 975 |     |  |
| Leu | Ala  | Leu | Gln | Pro | Gly | Pro  | Pro | Gly | Leu | His | Pro | Phe  | Pro | Phe | His |  |
|     |      | 980 |     |     |     |      |     | 985 |     |     |     |      | 990 |     |     |  |
| Pro | Ser  | Leu | Gly | Pro | Leu | Glu  | Arg | Glu | Arg | Leu | Ala | Leu  | Ala | Ala | Gly |  |
|     |      | 995 |     |     |     | 1000 |     |     |     |     |     | 1005 |     |     |     |  |
| Pro | Ala  | Leu | Arg | Pro | Asp | Met  | Ser | Tyr | Ala | Glu | Arg | Leu  | Ala | Ala |     |  |
|     | 1010 |     |     |     |     | 1015 |     |     |     |     |     | 1020 |     |     |     |  |
| Glu | Arg  | Gln | His | Ala | Glu | Arg  | Val | Ala | Ala | Leu | Gly | Asn  | Asp | Pro |     |  |
|     | 1025 |     |     |     |     | 1030 |     |     |     |     |     | 1035 |     |     |     |  |
| Leu | Ala  | Arg | Leu | Gln | Met | Leu  | Asn | Val | Thr | Pro | His | His  | His | Gln |     |  |
|     | 1040 |     |     |     |     | 1045 |     |     |     |     |     | 1050 |     |     |     |  |
| His | Ser  | His | Ile | His | Ser | His  | Leu | His | Leu | His | Gln | Gln  | Asp | Ala |     |  |
|     | 1055 |     |     |     |     | 1060 |     |     |     |     |     | 1065 |     |     |     |  |
| Ile | His  | Ala | Ala | Ser | Ala | Ser  | Val | His | Pro | Leu | Ile | Asp  | Pro | Leu |     |  |
|     | 1070 |     |     |     |     | 1075 |     |     |     |     |     | 1080 |     |     |     |  |

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Ala Ser Gly Ser His Leu Thr Arg Ile Pro Tyr Pro Ala Gly Thr  
 1085 1090 1095

Leu Pro Asn Pro Leu Leu Pro His Pro Leu His Glu Asn Glu Val  
 1100 1105 1110

Leu Arg His Gln Leu Phe Ala Ala Pro Tyr Arg Asp Leu Pro Ala  
 1115 1120 1125

Ser Leu Ser Ala Pro Met Ser Ala Ala His Gln Leu Gln Ala Met  
 1130 1135 1140

His Ala Gln Ser Ala Glu Leu Gln Arg Leu Ala Leu Glu Gln Gln  
 1145 1150 1155

Gln Trp Leu His Ala His His Pro Leu His Ser Val Pro Leu Pro  
 1160 1165 1170

Ala Gln Glu Asp Tyr Tyr Ser His Leu Lys Lys Glu Ser Asp Lys  
 1175 1180 1185

Pro Leu Ser Asx Met Ala  
 1190

&lt;210&gt; SEQ ID NO 54

&lt;211&gt; LENGTH: 4314

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Homo Sapiens

&lt;400&gt; SEQUENCE: 54

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cgagatcccg gggagccagc ttgctgggag agcgggacgg tccggagcaa gccagaggc      60
agaggaggcg acagagggaa aaagggccga gctagccgct ccagtgtgtg acaggagccg      120
aagggacgca ccacgccagc cccagcccgg ctccagcgac agccaacgcc tcttgacgag      180
cgggcggttc gaagccgccg cccggagctg ccttttcctc ttcggtgaag tttttaaag      240
ctgctaaaga ctcgagggaa gcaaggaaaag tgctgttagt gactgacggc tgcctttgtc      300
ctcctctctc ccaccccgcc tccccccacc ctgccttccc cccctcccc gtcttctctc      360
ccgcagctgc ctcactgcgc tactctcagc caacccccct caccaccctt cccccaccc      420
gccccccgc ccccgctggc ccagcgtgc cagcccgagt ttgcagagag gtaactccct      480
ttggctgcga gggggcgagc tagctgcaca ttgcaaagaa ggctcttagg agccaggcga      540
ctggggagcg gcttcagcac tgcagccagc acccgctgg ttaggctgca cgcggagaga      600
acctctgtt ttccccact ctctctccac ctctctctgc cttccccacc ccgagtggcg      660
agccagagat caaaagatga aaaggcagtc aggtcttcag tagccaaaaa acaaaacaaa      720
caaaaacaaa aaagccgaaa taaaagaaaa agataataac tcagttctta tttgcacct      780
cttcagtgga cactgaattt ggaagggtga ggattttgtt tttttctttt aagatctggg      840
catcttttga atctaccctt caagtattaa gagacagact gtgagcctag cagggcagat      900
cttgtccacc gtgtgtcttc ttctgcacga gactttgagg ctgtcagagc gctttttgag      960
tggttgctcc cgcaagtttc cttctctgga gcttcccgcg ggtgggcagc tagctgcagc      1020
gactaccgca tcatcacagc ctgttgaaact cttctgagca agagaagggg aggcggggta      1080
aggggaagtag gtggaagatt cagccaagct caaggatgga agtgagttta gggctgggaa      1140
gggtctaccc tcggcccgcc tccaagacct accgaggagc tttccagaat ctgttccaga      1200
gcgtgcgcga agtgatccag aacccggggc ccaggcacc agaggccgcg agcgcagcac      1260
ctcccgggcg cagtttctgt ctgctgcagc agcagcagca gcagcagcag cagcagcagc      1320
agcagcagca gcagcagcag cagcagcagc agcaagagac tagccccagg cagcagcagc      1380
agcagcaggg tgaggatggt tctccccaag cccatcgtag aggccccaca ggctacctgg      1440

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|                                                                     |      |
|---------------------------------------------------------------------|------|
| tcttgatga ggaacagcaa ccttcacagc cgcagtcggc cctggagtgc cccccgaga     | 1500 |
| gaggttgctg cccagagcct ggagccgccc tggccgccag caaggggctg ccgcagcagc   | 1560 |
| tgccagcacc tccggacgag gatgactcag ctgccccatc cacgttgctc ctgctgggccc  | 1620 |
| ccactttccc cggcttaagc agctgctccg ctgaccttaa agacatcctg agcgaggcca   | 1680 |
| gcaccatgca actccttcag caacagcagc aggaagcagt atccgaaggc agcagcagcg   | 1740 |
| ggagagcgag ggaggcctcg ggggctccca cttcctccaa ggacaattac ttagggggca   | 1800 |
| cttcgacctt ttctgacaac gccaaaggagt tgtgtaaggc agtgtcggtg tccatgggccc | 1860 |
| tgggtgtgga ggctgtggag catctgagtc cagggaaca gcttcggggg gattgcatgt    | 1920 |
| acgccccact ttgggaggtt ccaccgctg tgcgtccac tccttggtgc ccattggccc     | 1980 |
| aatgcaaagg ttctctgcta gacgacgag caggcaagag cactgaagat actgctgagt    | 2040 |
| attccccctt caaggagggt tacaccaaag ggctagaagg cgagagccta ggctgctctg   | 2100 |
| gcagcgtgc agcagggagc tccgggacac ttgaactgcc gtctaccctg tctctctaca    | 2160 |
| agtcgggagc actggacgag gcagctgctg accagagtcg cgactactac aactttccac   | 2220 |
| tggctctggc cggaccgccc cccctccgc cgcctccca tccccacgt cgcataaagc      | 2280 |
| tggagaaccc gctggactac ggcagcgctt gggcggtgc ggcggcgag tgcgctatg      | 2340 |
| gggacctggc gagcctgcat ggcgcgggtg cagcgggacc cggttctggg tcacctcag    | 2400 |
| ccgcgccttc ctcatcctgg cacactctct tcacagccga agaaggccag ttgtatggac   | 2460 |
| cgtgtggtgg tgggtggggg ggtggcgccg gcggcgccg cggcgccgccc ggcggcgccg   | 2520 |
| gcggcgccg cggcgaggcg ggagctgtag cccctacgg ctacactcg cccctcagg       | 2580 |
| ggctggcggg ccaggaaaag gacttcaccg cacctgatgt gtggtaccct ggcggcatgg   | 2640 |
| tgagcagagt gccctatccc agtcccactt gtgtcaaaag cgaaatgggc cctgggatgg   | 2700 |
| atagctactc cggaccttac ggggacatgc gtttgagagc tgcaggagc catgttttgc    | 2760 |
| ccattgacta ttactttcca cccagaaga cctgcctgat ctgtggagat gaagcttctg    | 2820 |
| ggtgtcacta tggagctctc acatgtggaa gctgcaaggc cttcttcaaa agagccgctg   | 2880 |
| aagggaaca gaagtacctg tgcgcagca gaaatgattg cactattgat aaattccgaa     | 2940 |
| ggaaaaattg tccatcttgt cgtcttcgga aatgttatga agcagggatg actctgggag   | 3000 |
| cccggaagct gaagaaactt ggtaacttga aactacagga ggaaggagag gcttcagca    | 3060 |
| ccaccagccc cactgaggag acaaccaga agctgacagt gtcacacatt gaaggctatg    | 3120 |
| aatgtcagcc catctttctg aatgtcctgg aagccattga gccagggtga gtgtgtgctg   | 3180 |
| gacacgacaa caaccagccc gactcctttg cagccttgct ctctagcctc aatgaactgg   | 3240 |
| gagagagaca gcttgtacac gtggtcaagt gggccaaggc cttgcctggc ttcgcaact    | 3300 |
| tacacgtgga cgaccagatg gctgtcatc agtactcctg gatggggctc atgggtgtttg   | 3360 |
| ccatgggctg gcgaccttc accaatgtca actccaggat gctctacttc gcccctgatc    | 3420 |
| tggttttcaa tgagtaccg atgcacaagt cccgatgta cagccagtgt gtccgaatga     | 3480 |
| ggcacctctc tcaagagttt ggatggctcc aaatcacccc ccaggaaatc ctgtgcatga   | 3540 |
| aagcactgct actcttcagc attattccag tggatgggct gaaaaatcaa aaattctttg   | 3600 |
| atgaacttcg aatgaactac atcaaggaa tcgatcgat cattgcatgc aaaagaaaaa     | 3660 |
| atccacatc ctgctcaaga cgcttctacc agctcaccaa gctcctggac tccgtgcagc    | 3720 |
| ctattgcgag agagctgcat cagttcactt ttgacctgct aatcaagtca cacatgggtga  | 3780 |
| gcgtggactt tccggaatg atggcagaga tcactctgt gcaagtgcc aagatccttt      | 3840 |

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ctgggaaagt caagcccatc tattccaca cccagtgaag cattggaaac cctatttccc 3900
caccgccagct catgccccct ttcagatgtc ttctgcctgt tataactctg cactactcct 3960
ctgcagtgcc ttggggaatt tcctctattg atgtacagtc tgtcatgaac atgttcctga 4020
attctatttg ctgggctttt tttttctctt tctctccttt ctttttcttc ttccctccct 4080
atctaaccct cccatggcac cttcagactt tgettcccat tgtggctcct atctgtgttt 4140
tgaatgggtgt tgtatgcctt taaatctgtg atgatcctca tatggcccag tgtcaagttg 4200
tgcttgttta cagcactact ctgtgccagc cacacaaacg tttacttacc ttatgccacg 4260
ggaagtttag agagctaaga ttatctgggg aaatcaaac aaaaacaagc aaac 4314

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&lt;210&gt; SEQ ID NO 55

&lt;211&gt; LENGTH: 920

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Homo Sapiens

&lt;400&gt; SEQUENCE: 55

```

Met Glu Val Gln Leu Gly Leu Gly Arg Val Tyr Pro Arg Pro Pro Ser
1           5           10           15
Lys Thr Tyr Arg Gly Ala Phe Gln Asn Leu Phe Gln Ser Val Arg Glu
20          25          30
Val Ile Gln Asn Pro Gly Pro Arg His Pro Glu Ala Ala Ser Ala Ala
35          40          45
Pro Pro Gly Ala Ser Leu Leu Leu Leu Gln Gln Gln Gln Gln Gln
50          55          60
Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln
65          70          75          80
Glu Thr Ser Pro Arg Gln Gln Gln Gln Gln Gln Gly Glu Asp Gly Ser
85          90          95
Pro Gln Ala His Arg Arg Gly Pro Thr Gly Tyr Leu Val Leu Asp Glu
100         105         110
Glu Gln Gln Pro Ser Gln Pro Gln Ser Ala Leu Glu Cys His Pro Glu
115         120         125
Arg Gly Cys Val Pro Glu Pro Gly Ala Ala Val Ala Ala Ser Lys Gly
130         135         140
Leu Pro Gln Gln Leu Pro Ala Pro Pro Asp Glu Asp Asp Ser Ala Ala
145         150         155         160
Pro Ser Thr Leu Ser Leu Leu Gly Pro Thr Phe Pro Gly Leu Ser Ser
165         170         175
Cys Ser Ala Asp Leu Lys Asp Ile Leu Ser Glu Ala Ser Thr Met Gln
180         185         190
Leu Leu Gln Gln Gln Gln Glu Ala Val Ser Glu Gly Ser Ser Ser
195         200         205
Gly Arg Ala Arg Glu Ala Ser Gly Ala Pro Thr Ser Ser Lys Asp Asn
210         215         220
Tyr Leu Gly Gly Thr Ser Thr Ile Ser Asp Asn Ala Lys Glu Leu Cys
225         230         235         240
Lys Ala Val Ser Val Ser Met Gly Leu Gly Val Glu Ala Leu Glu His
245         250         255
Leu Ser Pro Gly Glu Gln Leu Arg Gly Asp Cys Met Tyr Ala Pro Leu
260         265         270
Leu Gly Val Pro Pro Ala Val Arg Pro Thr Pro Cys Ala Pro Leu Ala
275         280         285
Glu Cys Lys Gly Ser Leu Leu Asp Asp Ser Ala Gly Lys Ser Thr Glu

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| 290                                                                                | 295 | 300 |
|------------------------------------------------------------------------------------|-----|-----|
| Asp Thr Ala Glu Tyr Ser Pro Phe Lys Gly Gly Tyr Thr Lys Gly Leu<br>305 310 315 320 |     |     |
| Glu Gly Glu Ser Leu Gly Cys Ser Gly Ser Ala Ala Ala Gly Ser Ser<br>325 330 335     |     |     |
| Gly Thr Leu Glu Leu Pro Ser Thr Leu Ser Leu Tyr Lys Ser Gly Ala<br>340 345 350     |     |     |
| Leu Asp Glu Ala Ala Ala Tyr Gln Ser Arg Asp Tyr Tyr Asn Phe Pro<br>355 360 365     |     |     |
| Leu Ala Leu Ala Gly Pro Pro Pro Pro Pro Pro Pro His Pro His<br>370 375 380         |     |     |
| Ala Arg Ile Lys Leu Glu Asn Pro Leu Asp Tyr Gly Ser Ala Trp Ala<br>385 390 395 400 |     |     |
| Ala Ala Ala Ala Gln Cys Arg Tyr Gly Asp Leu Ala Ser Leu His Gly<br>405 410 415     |     |     |
| Ala Gly Ala Ala Gly Pro Gly Ser Gly Ser Pro Ser Ala Ala Ala Ser<br>420 425 430     |     |     |
| Ser Ser Trp His Thr Leu Phe Thr Ala Glu Glu Gly Gln Leu Tyr Gly<br>435 440 445     |     |     |
| Pro Cys Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly<br>450 455 460         |     |     |
| Gly Gly Gly Gly Gly Gly Gly Gly Glu Ala Gly Ala Val Ala Pro<br>465 470 475 480     |     |     |
| Tyr Gly Tyr Thr Arg Pro Pro Gln Gly Leu Ala Gly Gln Glu Ser Asp<br>485 490 495     |     |     |
| Phe Thr Ala Pro Asp Val Trp Tyr Pro Gly Gly Met Val Ser Arg Val<br>500 505 510     |     |     |
| Pro Tyr Pro Ser Pro Thr Cys Val Lys Ser Glu Met Gly Pro Trp Met<br>515 520 525     |     |     |
| Asp Ser Tyr Ser Gly Pro Tyr Gly Asp Met Arg Leu Glu Thr Ala Arg<br>530 535 540     |     |     |
| Asp His Val Leu Pro Ile Asp Tyr Tyr Phe Pro Pro Gln Lys Thr Cys<br>545 550 555 560 |     |     |
| Leu Ile Cys Gly Asp Glu Ala Ser Gly Cys His Tyr Gly Ala Leu Thr<br>565 570 575     |     |     |
| Cys Gly Ser Cys Lys Val Phe Phe Lys Arg Ala Ala Glu Gly Lys Gln<br>580 585 590     |     |     |
| Lys Tyr Leu Cys Ala Ser Arg Asn Asp Cys Thr Ile Asp Lys Phe Arg<br>595 600 605     |     |     |
| Arg Lys Asn Cys Pro Ser Cys Arg Leu Arg Lys Cys Tyr Glu Ala Gly<br>610 615 620     |     |     |
| Met Thr Leu Gly Ala Arg Lys Leu Lys Lys Leu Gly Asn Leu Lys Leu<br>625 630 635 640 |     |     |
| Gln Glu Glu Gly Glu Ala Ser Ser Thr Thr Ser Pro Thr Glu Glu Thr<br>645 650 655     |     |     |
| Thr Gln Lys Leu Thr Val Ser His Ile Glu Gly Tyr Glu Cys Gln Pro<br>660 665 670     |     |     |
| Ile Phe Leu Asn Val Leu Glu Ala Ile Glu Pro Gly Val Val Cys Ala<br>675 680 685     |     |     |
| Gly His Asp Asn Asn Gln Pro Asp Ser Phe Ala Ala Leu Leu Ser Ser<br>690 695 700     |     |     |
| Leu Asn Glu Leu Gly Glu Arg Gln Leu Val His Val Val Lys Trp Ala<br>705 710 715 720 |     |     |

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Lys Ala Leu Pro Gly Phe Arg Asn Leu His Val Asp Asp Gln Met Ala  
                     725                                    730                                    735  
 Val Ile Gln Tyr Ser Trp Met Gly Leu Met Val Phe Ala Met Gly Trp  
                     740                                    745                                    750  
 Arg Ser Phe Thr Asn Val Asn Ser Arg Met Leu Tyr Phe Ala Pro Asp  
                     755                                    760                                    765  
 Leu Val Phe Asn Glu Tyr Arg Met His Lys Ser Arg Met Tyr Ser Gln  
                     770                                    775                                    780  
 Cys Val Arg Met Arg His Leu Ser Gln Glu Phe Gly Trp Leu Gln Ile  
                     785                                    790                                    795                                    800  
 Thr Pro Gln Glu Phe Leu Cys Met Lys Ala Leu Leu Leu Phe Ser Ile  
                     805                                    810                                    815  
 Ile Pro Val Asp Gly Leu Lys Asn Gln Lys Phe Phe Asp Glu Leu Arg  
                     820                                    825                                    830  
 Met Asn Tyr Ile Lys Glu Leu Asp Arg Ile Ile Ala Cys Lys Arg Lys  
                     835                                    840                                    845  
 Asn Pro Thr Ser Cys Ser Arg Arg Phe Tyr Gln Leu Thr Lys Leu Leu  
                     850                                    855                                    860  
 Asp Ser Val Gln Pro Ile Ala Arg Glu Leu His Gln Phe Thr Phe Asp  
                     865                                    870                                    875                                    880  
 Leu Leu Ile Lys Ser His Met Val Ser Val Asp Phe Pro Glu Met Met  
                     885                                    890                                    895  
 Ala Glu Ile Ile Ser Val Gln Val Pro Lys Ile Leu Ser Gly Lys Val  
                     900                                    905                                    910  
 Lys Pro Ile Tyr Phe His Thr Gln  
                     915                                    920

&lt;210&gt; SEQ ID NO 56

&lt;211&gt; LENGTH: 9435

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Homo Sapiens

&lt;400&gt; SEQUENCE: 56

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atggcgaccc tggaaaagct gatgaaggcc ttcgagtccc tcaagtcctt ccagcagcag      60
cagcagcagc agcagcagca gcagcagcag cagcagcagc agcagcagca gcagcaacag      120
ccgccaccgc cgccgcgcgc gccgcgcgct cctcagcttc ctcagccgcc gccgcaggca      180
cagccgctgc tgccctcagcc gcagccgccc ccgccgcgcg ccccgccgcc acccggcccg      240
gctgtggctg aggagccgct gcaccgacca aagaagaac ttctagctac caagaaagac      300
cgtgtgaatc attgtctgac aatatgtgaa aacatagtgg cacagtctgt cagaaattct      360
ccagaatttc agaaacttct gggcatcgct atggaacttt ttctgctgtg cagtgatgac      420
gcagagtcag atgtcaggat ggtggctgac gaatgcctca acaaagtat caaagctttg      480
atggattcta atcttccaag gttacagctc gagctctata aggaaattaa aaagaatggt      540
gccccctcga gtttgcgctg tgccctgtgg aggtttgctg agctggctca cctggttcgg      600
cctcagaaat gcaggcctta cctggtgaac cttctgccgt gcctgactcg aacaagcaag      660
agaccgaag aatcagtcca ggagacctg gctgcagctg ttcccaaat tatggcttct      720
tttggaatt ttgcaaatga caatgaaatt aaggttttgt taaaggcctt catagcgaac      780
ctgaagtcaa gctccccac cattcggcgg acagcggctg gatcagcagt gagcatctgc      840
cagcactcaa gaaggacaca atatttctat agttggctac taaatgtgct cttaggttta      900
ctcgttcctg tcgaggatga aactccact ctgctgattc ttggcgtgct gctcaccctg      960
aggtatttgg tgcccttctg gcagcagcag gtcaaggaca caagcctgaa aggcagcttc     1020

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|                                                                    |      |
|--------------------------------------------------------------------|------|
| ggagtgcaca ggaagaaat ggaagtctct ccttctgcag agcagcttgt ccaggtttat   | 1080 |
| gaactgacgt tacatcatat acagcaccaa gaccacaatg ttgtgaccgg agccctggag  | 1140 |
| ctgttgacgc agctcttcag aacgcctcca cccgagcttc tgcaaacctt gaccgcagtc  | 1200 |
| gggggcattg ggcagctcac cgctgctaag gaggagtctg gtggccgaag ccgtagtggg  | 1260 |
| agtattgtgg aacttatagc tggagggggg tctcatgca gccctgtcct ttcaagaaaa   | 1320 |
| caaaaaggca aagtgtctct aggagaagaa gaagccttgg aggatgactc tgaatcgaga  | 1380 |
| tcggatgtca gcagctctgc cttaacagcc tcagtgaagg atgagatcag tggagagctg  | 1440 |
| gctgtctctt caggggttct cactccaggg tcagcaggtc atgacatcat cacagaacag  | 1500 |
| ccacggtcac agcacacact gcaggcggac tcagtggatc tggccagctg tgacttgaca  | 1560 |
| agctctgcca ctgatgggga tgaggaggat atcttgagcc acagctccag ccaggtcagc  | 1620 |
| gccgtcccat ctgacctgc catggacctg aatgatggga cccaggcctc gtcgcccac    | 1680 |
| agcgacagct cccagaccac caccgaaggg cctgattcag ctgttacctt ttccagacag  | 1740 |
| tctgaaattg tgtagacggg taccgacaac cagtatttgg gcctgcagat tggacagccc  | 1800 |
| caggatgaag atgaggaagc cacaggtatt cttctgatg aagcctcgga ggccttcagg   | 1860 |
| aactcttcca tggcccttca acaggccatc ttattgaaaa acatgagtca ctgcaggcag  | 1920 |
| ccttctgaca gcagtgttga taaatttgtg ttgagagatg aagctactga accgggtgat  | 1980 |
| caagaaaaca agccttgccg catcaaaagt gacattggac agtccactga tgatgactct  | 2040 |
| gcacctcttg tccatttgtt ccgcctttta tctgtctcgt ttttgcctaa agggggaaaa  | 2100 |
| aatgtgtctg ttccggacag ggatgtgagg gtcagcgtga aggccttggc cctcagctgt  | 2160 |
| gtgggagcag ctgtggccct ccaccggaa tcttcttcca gcaaaactca taaagttcct   | 2220 |
| cttgacacca cgaatacccc tgaggaacag tatgtctcag acatcttgaa ctacatcgat  | 2280 |
| catggagacc cacaggttcg aggagccact gccattctct gtgggacctc catctgctcc  | 2340 |
| atcctcagca ggccccgctt ccacgtggga gattggatgg gcaccattag aacctcaca   | 2400 |
| ggaaatacat tttctttggc ggattgcatt cctttgctgc ggaaaacact gaaggatgag  | 2460 |
| tcttctgtta ctgtcaagtt agcttgatca gctgtgagga actgtgtcat gagtctctgc  | 2520 |
| agcagcagct acagtgagtt aggactgcag ctgatcatcg atgtgctgac tctgaggaac  | 2580 |
| agttcttatt ggctggtgag gacagagctt ctggaaaccc ttgcagagat tgacttcagg  | 2640 |
| ctggtgagct ttttgagggc aaaagcagaa aacttacaca gaggggctca tcattataca  | 2700 |
| gggcttttaa aactgcaaga acgagtgtct aataatgttg tcattccattt gcttgagat  | 2760 |
| gaagacccca ggggtgcgaca tgttgccgca gcataactaa ttaggcttgt cccaaagctg | 2820 |
| ttttataaat gtgaccaagg acaagctgat ccagttagtg ccgtggcaag agatcaaagc  | 2880 |
| agtgtttacc tgaaacttct catgcatgag acgcagcctc catctcattt ctccgtcagc  | 2940 |
| acaataacca gaatatatag aggcataaac ctactaccaa gcataacaga cgtcactatg  | 3000 |
| gaaaataaac tttcaagagt tattgcagca gtttctcatg aactaatcac atcaaccacc  | 3060 |
| agagcactca catttgatg ctgtgaagct ttgtgtcttc tttccactgc cttccagtt    | 3120 |
| tgcatattga gtttaggttg gcactgtgga gtgcctccac tgagtgcctc agatgagtct  | 3180 |
| aggaagagct gtaccgttgg gatggccaca atgattctga ccctgctctc gtcagcttgg  | 3240 |
| ttccatttgg atctctcagc ccatcaagat gctttgattt tggccggaaa cttgcttgca  | 3300 |
| gccagtgtc ccaaactctt gagaagttca tgggcctctg aagaagaagc caaccagca    | 3360 |
| gccaccaagc aagaggaggt ctggccagcc ctgggggacc gggccctggt gcccatggtg  | 3420 |

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|                                                                    |      |
|--------------------------------------------------------------------|------|
| gagcagctct tctctcacct gctgaaggtg attaacattt gtgcccacgt cctggatgac  | 3480 |
| gtggctcctg gacccgcaat aaaggcagcc ttgccttctc taacaaaccc cccttctcta  | 3540 |
| agtcccatcc gacgaaaggg gaaggagaaa gaaccaggag aacaagcatc tgtaccgttg  | 3600 |
| agteccaaga aaggcagtga ggccagtgca gcttctagac aatctgatac ctcaggctct  | 3660 |
| gttacaacaa gtaaactctc atcactgggg agtttctatc atcttccttc atacctcaaa  | 3720 |
| ctgcatgatg tcctgaaagc tacacacgct aactacaagg tcacgctgga tcttcagaac  | 3780 |
| agcacggaaa agtttgaggg gtttctccgc tcagccttg atgttcttctc tcagatacta  | 3840 |
| gagctggcca cactgcagga cattgggaag tgtgttgaag agatcctagg atacctgaaa  | 3900 |
| tctgcttta gtcgagaacc aatgatggca actgtttgtg ttcaacaatt gttgaagact   | 3960 |
| ctctttggca caaacttgcc ctcccagttt gatggcttat cttccaaccc cagcaagtca  | 4020 |
| caaggccgag cacagcgctc tggctcctcc agtgtgaggc caggcttgta ccactactgc  | 4080 |
| ttcatggccc cgtacaccca cttcacccag gccctcgtg acgccagcct gaggaacatg   | 4140 |
| gtgcaggcgg agcaggagaa cgacacctcg ggatggtttg atgtcctcca gaaagtgtct  | 4200 |
| accagttga agacaaacct cacgagtgtc acaaagaacc gtgcagataa gaatgctatt   | 4260 |
| cataatcaca ttcgtttgtt tgaacctctt gttataaaag ctttaaaaca gtacacgact  | 4320 |
| acaacatgtg tgcagttaca gaagcaggtt ttagatttgc tggcgagct ggttcagtta   | 4380 |
| cgggttaatt actgtcttct ggattcagat caggtgttta ttggctttgt attgaaacag  | 4440 |
| tttgaatata ttgaagtggg ccagttcagg gaatcagagg caatcattcc aaacatcttt  | 4500 |
| ttcttcttgg tattactatc ttatgaacgc tatcattcaa aacagatcat tggaattcct  | 4560 |
| aaaaatcattc agctctgtga tggcatcatg gccagtggaa ggaaggctgt gacacatgcc | 4620 |
| ataccggctc tgcagcccat agtccacgac ctctttgtat taagaggaaac aaataaagct | 4680 |
| gatgcaggaa aagagcttga aacccaaaa gaggtggtgg tgtcaatgtt actgagactc   | 4740 |
| atccagtacc atcaggtgtt ggagatgttc attcttgtcc tgcagcagtg ccacaaggag  | 4800 |
| aatgaagaca agtggaaagc actgtctcga cagatagctg acatcctcct cccaatgtta  | 4860 |
| gccaaacagc agatgcacat tgactctcat gaagcccttg gagtgttaaa tacattattt  | 4920 |
| gagatttttg ccccttcctc cctccgtccg gtagacatgc ttttacggag tatgttcgtc  | 4980 |
| actccaaaca caatggcgctc cgtgagcact gttcaactgt ggatatcggg aattctggcc | 5040 |
| attttgaggg ttctgatttc ccagtcact gaagatattg ttctttctcg tattcaggag   | 5100 |
| ctctccttct ctccgtattt aatctcctgt acagtaatta atagggttaag agatggggac | 5160 |
| agtacttcaa cgctagaaga acacagtga gggaaacaaa taaagaattt gccagaagaa   | 5220 |
| acattttcaa ggtttctatt acaactggtt ggtattcttt tagaagacat tgttacaaaa  | 5280 |
| cagctgaagg tggaaatgag tgagcagcaa catactttct attgccagga actaggcaca  | 5340 |
| ctgctaagt gtctgatcca catcttcaag tctggaatgt tccggagaat cacagcagct   | 5400 |
| gccactaggc tgttccgcag tgatggctgt ggcggcagtt tctacacct ggacagcttg   | 5460 |
| aacttgctgg ctcgttccat gatcaccacc caccggccc tgggtgtgct ctggtgtcag   | 5520 |
| atactgctgc ttgtcaacca caccgactac cgctggtggg cagaagtga gcagaccccg   | 5580 |
| aaaagacaca gtctgtccag cacaagtta cttagtcccc agatgtcttg agaagaggag   | 5640 |
| gattctgact tggcagccaa acttggaatg tgcaatagag aaatagtacg aagaggggct  | 5700 |
| ctcattctct tctgtgatta tgtctgtcag aacctccatg actccgagca cttaacgtgg  | 5760 |
| ctcattgtaa atcacattca agatctgatc agcctttccc acgagcctcc agtacaggac  | 5820 |

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|            |            |            |            |            |            |      |
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| tctcgttgt  | aaaaccttc  | aactccaac  | atgctgaaga | aaactctca  | gtgcttgag  | 5940 |
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| acccctttcc | gtgtgctggc | tcgcatggtc | gacatccttg | cttgctgccg | ggtagaaatg | 6060 |
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| ctggacaggt | tctgtctctc | caccatgcaa | gactcactta | gtccctctcc | tccagtctct | 6240 |
| ttccacccgc | tggacgggga | tgggcacgtg | tcactggaaa | cagtgaagtc | ggacaaagac | 6300 |
| tggtagcttc | atcttgctca | atcccagtg  | tggaccaggt | cagattctgc | actgctggaa | 6360 |
| ggtgcagagc | tggtagaatc | gattcctgct | gaagatatga | atgccttcat | gatgaactcg | 6420 |
| gagttcaacc | taagcctgct | agctccatgc | ttaagcctag | ggatgagtg  | aatttctggt | 6480 |
| ggccagaaga | gtgccctttt | tgaagcagcc | cgtgaggtga | ctctggcccg | tgtgagcggc | 6540 |
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| tccaggaaac | accgggctgg | agttgacatc | cactcctggt | cgcagttttt | gcttgagttg | 8040 |
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| gaggtggtca | gatcccttct | agtgtgtcca | gacttgttca | ccgagcgcaa | ccagtttgag | 8160 |
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&lt;210&gt; SEQ ID NO 57

&lt;211&gt; LENGTH: 3144

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Homo Sapiens

&lt;400&gt; SEQUENCE: 57

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Met Ala Thr Leu Glu Lys Leu Met Lys Ala Phe Glu Ser Leu Lys Ser
1           5           10           15
Phe Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln
20           25           30
Gln Gln Gln Gln Gln Gln Gln Gln Pro Pro Pro Pro Pro Pro Pro Pro
35           40           45
Pro Pro Pro Gln Leu Pro Gln Pro Pro Pro Gln Ala Gln Pro Leu Leu
50           55           60
Pro Gln Pro Gln Pro Pro Pro Pro Pro Pro Pro Pro Pro Gly Pro
65           70           75           80
Ala Val Ala Glu Glu Pro Leu His Arg Pro Lys Lys Glu Leu Ser Ala
85           90           95
Thr Lys Lys Asp Arg Val Asn His Cys Leu Thr Ile Cys Glu Asn Ile
100          105          110
Val Ala Gln Ser Val Arg Asn Ser Pro Glu Phe Gln Lys Leu Leu Gly
115          120          125
Ile Ala Met Glu Leu Phe Leu Leu Cys Ser Asp Asp Ala Glu Ser Asp
130          135          140
Val Arg Met Val Ala Asp Glu Cys Leu Asn Lys Val Ile Lys Ala Leu
145          150          155          160

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|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Asp | Ser | Asn | Leu | Pro | Arg | Leu | Gln | Leu | Glu | Leu | Tyr | Lys | Glu | Ile |
|     |     |     |     | 165 |     |     |     |     |     | 170 |     |     |     | 175 |     |
| Lys | Lys | Asn | Gly | Ala | Pro | Arg | Ser | Leu | Arg | Ala | Ala | Leu | Trp | Arg | Phe |
|     |     |     | 180 |     |     |     |     | 185 |     |     |     |     | 190 |     |     |
| Ala | Glu | Leu | Ala | His | Leu | Val | Arg | Pro | Gln | Lys | Cys | Arg | Pro | Tyr | Leu |
|     |     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |
| Val | Asn | Leu | Leu | Pro | Cys | Leu | Thr | Arg | Thr | Ser | Lys | Arg | Pro | Glu | Glu |
|     | 210 |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |
| Ser | Val | Gln | Glu | Thr | Leu | Ala | Ala | Ala | Val | Pro | Lys | Ile | Met | Ala | Ser |
| 225 |     |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |
| Phe | Gly | Asn | Phe | Ala | Asn | Asp | Asn | Glu | Ile | Lys | Val | Leu | Leu | Lys | Ala |
|     |     |     |     | 245 |     |     |     |     | 250 |     |     |     |     | 255 |     |
| Phe | Ile | Ala | Asn | Leu | Lys | Ser | Ser | Ser | Pro | Thr | Ile | Arg | Arg | Thr | Ala |
|     |     |     | 260 |     |     |     |     | 265 |     |     |     |     | 270 |     |     |
| Ala | Gly | Ser | Ala | Val | Ser | Ile | Cys | Gln | His | Ser | Arg | Arg | Thr | Gln | Tyr |
|     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |
| Phe | Tyr | Ser | Trp | Leu | Leu | Asn | Val | Leu | Leu | Gly | Leu | Leu | Val | Pro | Val |
|     | 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |
| Glu | Asp | Glu | His | Ser | Thr | Leu | Leu | Ile | Leu | Gly | Val | Leu | Leu | Thr | Leu |
| 305 |     |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |
| Arg | Tyr | Leu | Val | Pro | Leu | Leu | Gln | Gln | Gln | Val | Lys | Asp | Thr | Ser | Leu |
|     |     |     |     | 325 |     |     |     |     | 330 |     |     |     |     | 335 |     |
| Lys | Gly | Ser | Phe | Gly | Val | Thr | Arg | Lys | Glu | Met | Glu | Val | Ser | Pro | Ser |
|     |     |     | 340 |     |     |     |     | 345 |     |     |     |     | 350 |     |     |
| Ala | Glu | Gln | Leu | Val | Gln | Val | Tyr | Glu | Leu | Thr | Leu | His | His | Thr | Gln |
|     |     | 355 |     |     |     |     | 360 |     |     |     |     | 365 |     |     |     |
| His | Gln | Asp | His | Asn | Val | Val | Thr | Gly | Ala | Leu | Glu | Leu | Leu | Gln | Gln |
|     | 370 |     |     |     | 375 |     |     |     |     |     | 380 |     |     |     |     |
| Leu | Phe | Arg | Thr | Pro | Pro | Glu | Leu | Leu | Gln | Thr | Leu | Thr | Ala | Val |     |
| 385 |     |     |     | 390 |     |     |     |     | 395 |     |     |     |     | 400 |     |
| Gly | Gly | Ile | Gly | Gln | Leu | Thr | Ala | Ala | Lys | Glu | Glu | Ser | Gly | Gly | Arg |
|     |     |     | 405 |     |     |     |     |     | 410 |     |     |     |     | 415 |     |
| Ser | Arg | Ser | Gly | Ser | Ile | Val | Glu | Leu | Ile | Ala | Gly | Gly | Gly | Ser | Ser |
|     |     |     | 420 |     |     |     |     | 425 |     |     |     |     | 430 |     |     |
| Cys | Ser | Pro | Val | Leu | Ser | Arg | Lys | Gln | Lys | Gly | Lys | Val | Leu | Leu | Gly |
|     |     | 435 |     |     |     |     | 440 |     |     |     |     | 445 |     |     |     |
| Glu | Glu | Glu | Ala | Leu | Glu | Asp | Asp | Ser | Glu | Ser | Arg | Ser | Asp | Val | Ser |
|     |     | 450 |     |     |     | 455 |     |     |     |     | 460 |     |     |     |     |
| Ser | Ser | Ala | Leu | Thr | Ala | Ser | Val | Lys | Asp | Glu | Ile | Ser | Gly | Glu | Leu |
| 465 |     |     |     |     | 470 |     |     |     |     | 475 |     |     |     |     | 480 |
| Ala | Ala | Ser | Ser | Gly | Val | Ser | Thr | Pro | Gly | Ser | Ala | Gly | His | Asp | Ile |
|     |     |     |     | 485 |     |     |     |     | 490 |     |     |     |     | 495 |     |
| Ile | Thr | Glu | Gln | Pro | Arg | Ser | Gln | His | Thr | Leu | Gln | Ala | Asp | Ser | Val |
|     |     |     | 500 |     |     |     |     | 505 |     |     |     |     | 510 |     |     |
| Asp | Leu | Al  |     |     |     |     |     |     |     |     |     |     |     |     |     |

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| 580                                                                                | 585 | 590 |
|------------------------------------------------------------------------------------|-----|-----|
| Leu Gly Leu Gln Ile Gly Gln Pro Gln Asp Glu Asp Glu Glu Ala Thr<br>595 600 605     |     |     |
| Gly Ile Leu Pro Asp Glu Ala Ser Glu Ala Phe Arg Asn Ser Ser Met<br>610 615 620     |     |     |
| Ala Leu Gln Gln Ala His Leu Leu Lys Asn Met Ser His Cys Arg Gln<br>625 630 635 640 |     |     |
| Pro Ser Asp Ser Ser Val Asp Lys Phe Val Leu Arg Asp Glu Ala Thr<br>645 650 655     |     |     |
| Glu Pro Gly Asp Gln Glu Asn Lys Pro Cys Arg Ile Lys Gly Asp Ile<br>660 665 670     |     |     |
| Gly Gln Ser Thr Asp Asp Asp Ser Ala Pro Leu Val His Cys Val Arg<br>675 680 685     |     |     |
| Leu Leu Ser Ala Ser Phe Leu Leu Thr Gly Gly Lys Asn Val Leu Val<br>690 695 700     |     |     |
| Pro Asp Arg Asp Val Arg Val Ser Val Lys Ala Leu Ala Leu Ser Cys<br>705 710 715 720 |     |     |
| Val Gly Ala Ala Val Ala Leu His Pro Glu Ser Phe Phe Ser Lys Leu<br>725 730 735     |     |     |
| Tyr Lys Val Pro Leu Asp Thr Thr Glu Tyr Pro Glu Glu Gln Tyr Val<br>740 745 750     |     |     |
| Ser Asp Ile Leu Asn Tyr Ile Asp His Gly Asp Pro Gln Val Arg Gly<br>755 760 765     |     |     |
| Ala Thr Ala Ile Leu Cys Gly Thr Leu Ile Cys Ser Ile Leu Ser Arg<br>770 775 780     |     |     |
| Ser Arg Phe His Val Gly Asp Trp Met Gly Thr Ile Arg Thr Leu Thr<br>785 790 795 800 |     |     |
| Gly Asn Thr Phe Ser Leu Ala Asp Cys Ile Pro Leu Leu Arg Lys Thr<br>805 810 815     |     |     |
| Leu Lys Asp Glu Ser Ser Val Thr Cys Lys Leu Ala Cys Thr Ala Val<br>820 825 830     |     |     |
| Arg Asn Cys Val Met Ser Leu Cys Ser Ser Ser Tyr Ser Glu Leu Gly<br>835 840 845     |     |     |
| Leu Gln Leu Ile Ile Asp Val Leu Thr Leu Arg Asn Ser Ser Tyr Trp<br>850 855 860     |     |     |
| Leu Val Arg Thr Glu Leu Leu Glu Thr Leu Ala Glu Ile Asp Phe Arg<br>865 870 875 880 |     |     |
| Leu Val Ser Phe Leu Glu Ala Lys Ala Glu Asn Leu His Arg Gly Ala<br>885 890 895     |     |     |
| His His Tyr Thr Gly Leu Leu Lys Leu Gln Glu Arg Val Leu Asn Asn<br>900 905 910     |     |     |
| Val Val Ile His Leu Leu Gly Asp Glu Asp Pro Arg Val Arg His Val<br>915 920 925     |     |     |
| Ala Ala Ala Ser Leu Ile Arg Leu Val Pro Lys Leu Phe Tyr Lys Cys<br>930 935 940     |     |     |
| Asp Gln Gly Gln Ala Asp Pro Val Val Ala Val Ala Arg Asp Gln Ser<br>945 950 955 960 |     |     |
| Ser Val Tyr Leu Lys Leu Leu Met His Glu Thr Gln Pro Pro Ser His<br>965 970 975     |     |     |
| Phe Ser Val Ser Thr Ile Thr Arg Ile Tyr Arg Gly Tyr Asn Leu Leu<br>980 985 990     |     |     |
| Pro Ser Ile Thr Asp Val Thr Met Glu Asn Asn Leu Ser Arg Val Ile<br>995 1000 1005   |     |     |

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|      |     |     |     |     |     |      |     |     |     |     |      |     |     |     |
|------|-----|-----|-----|-----|-----|------|-----|-----|-----|-----|------|-----|-----|-----|
| Ala  | Ala | Val | Ser | His | Glu | Leu  | Ile | Thr | Ser | Thr | Thr  | Arg | Ala | Leu |
| 1010 |     |     |     |     |     | 1015 |     |     |     |     | 1020 |     |     |     |
| Thr  | Phe | Gly | Cys | Cys | Glu | Ala  | Leu | Cys | Leu | Leu | Ser  | Thr | Ala | Phe |
| 1025 |     |     |     |     |     | 1030 |     |     |     |     | 1035 |     |     |     |
| Pro  | Val | Cys | Ile | Trp | Ser | Leu  | Gly | Trp | His | Cys | Gly  | Val | Pro | Pro |
| 1040 |     |     |     |     |     | 1045 |     |     |     |     | 1050 |     |     |     |
| Leu  | Ser | Ala | Ser | Asp | Glu | Ser  | Arg | Lys | Ser | Cys | Thr  | Val | Gly | Met |
| 1055 |     |     |     |     |     | 1060 |     |     |     |     | 1065 |     |     |     |
| Ala  | Thr | Met | Ile | Leu | Thr | Leu  | Leu | Ser | Ser | Ala | Trp  | Phe | Pro | Leu |
| 1070 |     |     |     |     |     | 1075 |     |     |     |     | 1080 |     |     |     |
| Asp  | Leu | Ser | Ala | His | Gln | Asp  | Ala | Leu | Ile | Leu | Ala  | Gly | Asn | Leu |
| 1085 |     |     |     |     |     | 1090 |     |     |     |     | 1095 |     |     |     |
| Leu  | Ala | Ala | Ser | Ala | Pro | Lys  | Ser | Leu | Arg | Ser | Ser  | Trp | Ala | Ser |
| 1100 |     |     |     |     |     | 1105 |     |     |     |     | 1110 |     |     |     |
| Glu  | Glu | Glu | Ala | Asn | Pro | Ala  | Ala | Thr | Lys | Gln | Glu  | Glu | Val | Trp |
| 1115 |     |     |     |     |     | 1120 |     |     |     |     | 1125 |     |     |     |
| Pro  | Ala | Leu | Gly | Asp | Arg | Ala  | Leu | Val | Pro | Met | Val  | Glu | Gln | Leu |
| 1130 |     |     |     |     |     | 1135 |     |     |     |     | 1140 |     |     |     |
| Phe  | Ser | His | Leu | Leu | Lys | Val  | Ile | Asn | Ile | Cys | Ala  | His | Val | Leu |
| 1145 |     |     |     |     |     | 1150 |     |     |     |     | 1155 |     |     |     |
| Asp  | Asp | Val | Ala | Pro | Gly | Pro  | Ala | Ile | Lys | Ala | Ala  | Leu | Pro | Ser |
| 1160 |     |     |     |     |     | 1165 |     |     |     |     | 1170 |     |     |     |
| Leu  | Thr | Asn | Pro | Pro | Ser | Leu  | Ser | Pro | Ile | Arg | Arg  | Lys | Gly | Lys |
| 1175 |     |     |     |     |     | 1180 |     |     |     |     | 1185 |     |     |     |
| Glu  | Lys | Glu | Pro | Gly | Glu | Gln  | Ala | Ser | Val | Pro | Leu  | Ser | Pro | Lys |
| 1190 |     |     |     |     |     | 1195 |     |     |     |     | 1200 |     |     |     |
| Lys  | Gly | Ser | Glu | Ala | Ser | Ala  | Ala | Ser | Arg | Gln | Ser  | Asp | Thr | Ser |
| 1205 |     |     |     |     |     | 1210 |     |     |     |     | 1215 |     |     |     |
| Gly  | Pro | Val | Thr | Thr | Ser | Lys  | Ser | Ser | Ser | Leu | Gly  | Ser | Phe | Tyr |
| 1220 |     |     |     |     |     | 1225 |     |     |     |     | 1230 |     |     |     |
| His  | Leu | Pro | Ser | Tyr | Leu | Lys  | Leu | His | Asp | Val | Leu  | Lys | Ala | Thr |
| 1235 |     |     |     |     |     | 1240 |     |     |     |     | 1245 |     |     |     |
| His  | Ala | Asn | Tyr | Lys | Val | Thr  | Leu | Asp | Leu | Gln | Asn  | Ser | Thr | Glu |
| 1250 |     |     |     |     |     | 1255 |     |     |     |     | 1260 |     |     |     |
| Lys  | Phe | Gly | Gly | Phe | Leu | Arg  | Ser | Ala | Leu | Asp | Val  | Leu | Ser | Gln |
| 1265 |     |     |     |     |     | 1270 |     |     |     |     | 1275 |     |     |     |
| Ile  | Leu | Glu | Leu | Ala | Thr | Leu  | Gln | Asp | Ile | Gly | Lys  | Cys | Val | Glu |
| 1280 |     |     |     |     |     | 1285 |     |     |     |     | 1290 |     |     |     |
| Glu  | Ile | Leu | Gly | Tyr | Leu | Lys  | Ser | Cys | Phe | Ser | Arg  | Glu | Pro | Met |
| 1295 |     |     |     |     |     | 1300 |     |     |     |     | 1305 |     |     |     |
| Met  | Ala | Thr | Val | Cys | Val | Gln  | Gln | Leu | Leu | Lys | Thr  | Leu | Phe | Gly |
| 1310 |     |     |     |     |     | 1315 |     |     |     |     | 1320 |     |     |     |
| Thr  | Asn | Leu | Ala | Ser | Gln | Phe  | Asp | Gly | Leu | Ser | Ser  | Asn | Pro | Ser |
| 1325 |     |     |     |     |     | 1330 |     |     |     |     | 1335 |     |     |     |
| Lys  | Ser | Gln | Gly | Arg | Ala | Gln  | Arg | Leu | Gly | Ser | Ser  | Ser | Val | Arg |
| 1340 |     |     |     |     |     | 1345 |     |     |     |     | 1350 |     |     |     |
| Pro  | Gly | Leu | Tyr | His | Tyr | Cys  | Phe | Met | Ala | Pro | Tyr  | Thr | His | Phe |
| 1355 |     |     |     |     |     | 1360 |     |     |     |     | 1365 |     |     |     |
| Thr  | Gln | Ala | Leu | Ala | Asp | Ala  | Ser | Leu | Arg | Asn | Met  | Val | Gln | Ala |
| 1370 |     |     |     |     |     | 1375 |     |     |     |     | 1380 |     |     |     |
| Glu  | Gln | Glu | Asn | Asp | Thr | Ser  | Gly | Trp | Phe | Asp | Val  | Leu | Gln | Lys |
| 1385 |     |     |     |     |     | 1390 |     |     |     |     | 1395 |     |     |     |
| Val  | Ser | Thr | Gln | Leu | Lys | Thr  | Asn | Leu | Thr | Ser | Val  | Thr | Lys | Asn |
| 1400 |     |     |     |     |     | 1405 |     |     |     |     | 1410 |     |     |     |

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|         |                 |      |                 |                 |             |
|---------|-----------------|------|-----------------|-----------------|-------------|
| Arg Ala | Asp Lys Asn Ala | Ile  | His Asn His     | Ile Arg         | Leu Phe Glu |
| 1415    |                 | 1420 |                 | 1425            |             |
| Pro Leu | Val Ile Lys Ala | Leu  | Lys Gln Tyr Thr | Thr Thr Cys     |             |
| 1430    |                 | 1435 |                 | 1440            |             |
| Val Gln | Leu Gln Lys Gln | Val  | Leu Asp Leu Leu | Ala Gln Leu Val |             |
| 1445    |                 | 1450 |                 | 1455            |             |
| Gln Leu | Arg Val Asn Tyr | Cys  | Leu Leu Asp Ser | Asp Gln Val Phe |             |
| 1460    |                 | 1465 |                 | 1470            |             |
| Ile Gly | Phe Val Leu Lys | Gln  | Phe Glu Tyr Ile | Glu Val Gly Gln |             |
| 1475    |                 | 1480 |                 | 1485            |             |
| Phe Arg | Glu Ser Glu Ala | Ile  | Ile Pro Asn Ile | Phe Phe Phe Leu |             |
| 1490    |                 | 1495 |                 | 1500            |             |
| Val Leu | Leu Ser Tyr Glu | Arg  | Tyr His Ser Lys | Gln Ile Ile Gly |             |
| 1505    |                 | 1510 |                 | 1515            |             |
| Ile Pro | Lys Ile Ile Gln | Leu  | Cys Asp Gly Ile | Met Ala Ser Gly |             |
| 1520    |                 | 1525 |                 | 1530            |             |
| Arg Lys | Ala Val Thr His | Ala  | Ile Pro Ala Leu | Gln Pro Ile Val |             |
| 1535    |                 | 1540 |                 | 1545            |             |
| His Asp | Leu Phe Val Leu | Arg  | Gly Thr Asn Lys | Ala Asp Ala Gly |             |
| 1550    |                 | 1555 |                 | 1560            |             |
| Lys Glu | Leu Glu Thr Gln | Lys  | Glu Val Val Val | Ser Met Leu Leu |             |
| 1565    |                 | 1570 |                 | 1575            |             |
| Arg Leu | Ile Gln Tyr His | Gln  | Val Leu Glu Met | Phe Ile Leu Val |             |
| 1580    |                 | 1585 |                 | 1590            |             |
| Leu Gln | Gln Cys His Lys | Glu  | Asn Glu Asp Lys | Trp Lys Arg Leu |             |
| 1595    |                 | 1600 |                 | 1605            |             |
| Ser Arg | Gln Ile Ala Asp | Ile  | Ile Leu Pro Met | Leu Ala Lys Gln |             |
| 1610    |                 | 1615 |                 | 1620            |             |
| Gln Met | His Ile Asp Ser | His  | Glu Ala Leu Gly | Val Leu Asn Thr |             |
| 1625    |                 | 1630 |                 | 1635            |             |
| Leu Phe | Glu Ile Leu Ala | Pro  | Ser Ser Leu Arg | Pro Val Asp Met |             |
| 1640    |                 | 1645 |                 | 1650            |             |
| Leu Leu | Arg Ser Met Phe | Val  | Thr Pro Asn Thr | Met Ala Ser Val |             |
| 1655    |                 | 1660 |                 | 1665            |             |
| Ser Thr | Val Gln Leu Trp | Ile  | Ser Gly Ile Leu | Ala Ile Leu Arg |             |
| 1670    |                 | 1675 |                 | 1680            |             |
| Val Leu | Ile Ser Gln Ser | Thr  | Glu Asp Ile Val | Leu Ser Arg Ile |             |
| 1685    |                 | 1690 |                 | 1695            |             |
| Gln Glu | Leu Ser Phe Ser | Pro  | Tyr Leu Ile Ser | Cys Thr Val Ile |             |
| 1700    |                 | 1705 |                 | 1710            |             |
| Asn Arg | Leu Arg Asp Gly | Asp  | Ser Thr Ser Thr | Leu Glu Glu His |             |
| 1715    |                 | 1720 |                 | 1725            |             |
| Ser Glu | Gly Lys Gln Ile | Lys  | Asn Leu Pro Glu | Glu Thr Phe Ser |             |
| 1730    |                 | 1735 |                 | 1740            |             |
| Arg Phe | Leu Leu Gln Leu | Val  | Gly Ile Leu Leu | Glu Asp Ile Val |             |
| 1745    |                 | 1750 |                 | 1755            |             |
| Thr Lys | Gln Leu Lys Val | Glu  | Met Ser Glu Gln | Gln His Thr Phe |             |
| 1760    |                 | 1765 |                 | 1770            |             |
| Tyr Cys | Gln Glu Leu Gly | Thr  | Leu Leu Met Cys | Leu Ile His Ile |             |
| 1775    |                 | 1780 |                 | 1785            |             |
| Phe Lys | Ser Gly Met Phe | Arg  | Arg Ile Thr Ala | Ala Ala Thr Arg |             |
| 1790    |                 | 1795 |                 | 1800            |             |
| Leu Phe | Arg Ser Asp Gly | Cys  | Gly Gly Ser Phe | Tyr Thr Leu Asp |             |

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|                                                             |      |      |
|-------------------------------------------------------------|------|------|
| 1805                                                        | 1810 | 1815 |
| Ser Leu Asn Leu Arg Ala Arg Ser Met Ile Thr Thr His Pro Ala |      |      |
| 1820                                                        | 1825 | 1830 |
| Leu Val Leu Leu Trp Cys Gln Ile Leu Leu Leu Val Asn His Thr |      |      |
| 1835                                                        | 1840 | 1845 |
| Asp Tyr Arg Trp Trp Ala Glu Val Gln Gln Thr Pro Lys Arg His |      |      |
| 1850                                                        | 1855 | 1860 |
| Ser Leu Ser Ser Thr Lys Leu Leu Ser Pro Gln Met Ser Gly Glu |      |      |
| 1865                                                        | 1870 | 1875 |
| Glu Glu Asp Ser Asp Leu Ala Ala Lys Leu Gly Met Cys Asn Arg |      |      |
| 1880                                                        | 1885 | 1890 |
| Glu Ile Val Arg Arg Gly Ala Leu Ile Leu Phe Cys Asp Tyr Val |      |      |
| 1895                                                        | 1900 | 1905 |
| Cys Gln Asn Leu His Asp Ser Glu His Leu Thr Trp Leu Ile Val |      |      |
| 1910                                                        | 1915 | 1920 |
| Asn His Ile Gln Asp Leu Ile Ser Leu Ser His Glu Pro Pro Val |      |      |
| 1925                                                        | 1930 | 1935 |
| Gln Asp Phe Ile Ser Ala Val His Arg Asn Ser Ala Ala Ser Gly |      |      |
| 1940                                                        | 1945 | 1950 |
| Leu Phe Ile Gln Ala Ile Gln Ser Arg Cys Glu Asn Leu Ser Thr |      |      |
| 1955                                                        | 1960 | 1965 |
| Pro Thr Met Leu Lys Lys Thr Leu Gln Cys Leu Glu Gly Ile His |      |      |
| 1970                                                        | 1975 | 1980 |
| Leu Ser Gln Ser Gly Ala Val Leu Thr Leu Tyr Val Asp Arg Leu |      |      |
| 1985                                                        | 1990 | 1995 |
| Leu Cys Thr Pro Phe Arg Val Leu Ala Arg Met Val Asp Ile Leu |      |      |
| 2000                                                        | 2005 | 2010 |
| Ala Cys Arg Arg Val Glu Met Leu Leu Ala Ala Asn Leu Gln Ser |      |      |
| 2015                                                        | 2020 | 2025 |
| Ser Met Ala Gln Leu Pro Met Glu Glu Leu Asn Arg Ile Gln Glu |      |      |
| 2030                                                        | 2035 | 2040 |
| Tyr Leu Gln Ser Ser Gly Leu Ala Gln Arg His Gln Arg Leu Tyr |      |      |
| 2045                                                        | 2050 | 2055 |
| Ser Leu Leu Asp Arg Phe Arg Leu Ser Thr Met Gln Asp Ser Leu |      |      |
| 2060                                                        | 2065 | 2070 |
| Ser Pro Ser Pro Pro Val Ser Ser His Pro Leu Asp Gly Asp Gly |      |      |
| 2075                                                        | 2080 | 2085 |
| His Val Ser Leu Glu Thr Val Ser Pro Asp Lys Asp Trp Tyr Val |      |      |
| 2090                                                        | 2095 | 2100 |
| His Leu Val Lys Ser Gln Cys Trp Thr Arg Ser Asp Ser Ala Leu |      |      |
| 2105                                                        | 2110 | 2115 |
| Leu Glu Gly Ala Glu Leu Val Asn Arg Ile Pro Ala Glu Asp Met |      |      |
| 2120                                                        | 2125 | 2130 |
| Asn Ala Phe Met Met Asn Ser Glu Phe Asn Leu Ser Leu Leu Ala |      |      |
| 2135                                                        | 2140 | 2145 |
| Pro Cys Leu Ser Leu Gly Met Ser Glu Ile Ser Gly Gly Gln Lys |      |      |
| 2150                                                        | 2155 | 2160 |
| Ser Ala Leu Phe Glu Ala Ala Arg Glu Val Thr Leu Ala Arg Val |      |      |
| 2165                                                        | 2170 | 2175 |
| Ser Gly Thr Val Gln Gln Leu Pro Ala Val His His Val Phe Gln |      |      |
| 2180                                                        | 2185 | 2190 |
| Pro Glu Leu Pro Ala Glu Pro Ala Ala Tyr Trp Ser Lys Leu Asn |      |      |
| 2195                                                        | 2200 | 2205 |

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|         |         |         |      |         |         |      |         |     |  |
|---------|---------|---------|------|---------|---------|------|---------|-----|--|
| Asp Leu | Phe Gly | Asp Ala | Ala  | Leu Tyr | Gln Ser | Leu  | Pro Thr | Leu |  |
| 2210    |         |         | 2215 |         |         | 2220 |         |     |  |
| Ala Arg | Ala Leu | Ala Gln | Tyr  | Leu Val | Val Val | Ser  | Lys Leu | Pro |  |
| 2225    |         |         | 2230 |         |         | 2235 |         |     |  |
| Ser His | Leu His | Leu Pro | Pro  | Glu Lys | Glu Lys | Asp  | Ile Val | Lys |  |
| 2240    |         |         | 2245 |         |         | 2250 |         |     |  |
| Phe Val | Val Ala | Thr Leu | Glu  | Ala Leu | Ser Trp | His  | Leu Ile | His |  |
| 2255    |         |         | 2260 |         |         | 2265 |         |     |  |
| Glu Gln | Ile Pro | Leu Ser | Leu  | Asp Leu | Gln Ala | Gly  | Leu Asp | Cys |  |
| 2270    |         |         | 2275 |         |         | 2280 |         |     |  |
| Cys Cys | Leu Ala | Leu Gln | Leu  | Pro Gly | Leu Trp | Ser  | Val Val | Ser |  |
| 2285    |         |         | 2290 |         |         | 2295 |         |     |  |
| Ser Thr | Glu Phe | Val Thr | His  | Ala Cys | Ser Leu | Ile  | Tyr Cys | Val |  |
| 2300    |         |         | 2305 |         |         | 2310 |         |     |  |
| His Phe | Ile Leu | Glu Ala | Val  | Ala Val | Gln Pro | Gly  | Glu Gln | Leu |  |
| 2315    |         |         | 2320 |         |         | 2325 |         |     |  |
| Leu Ser | Pro Glu | Arg Arg | Thr  | Asn Thr | Pro Lys | Ala  | Ile Ser | Glu |  |
| 2330    |         |         | 2335 |         |         | 2340 |         |     |  |
| Glu Glu | Glu Glu | Val Asp | Pro  | Asn Thr | Gln Asn | Pro  | Lys Tyr | Ile |  |
| 2345    |         |         | 2350 |         |         | 2355 |         |     |  |
| Thr Ala | Ala Cys | Glu Met | Val  | Ala Glu | Met Val | Glu  | Ser Leu | Gln |  |
| 2360    |         |         | 2365 |         |         | 2370 |         |     |  |
| Ser Val | Leu Ala | Leu Gly | His  | Lys Arg | Asn Ser | Gly  | Val Pro | Ala |  |
| 2375    |         |         | 2380 |         |         | 2385 |         |     |  |
| Phe Leu | Thr Pro | Leu Leu | Arg  | Asn Ile | Ile Ile | Ser  | Leu Ala | Arg |  |
| 2390    |         |         | 2395 |         |         | 2400 |         |     |  |
| Leu Pro | Leu Val | Asn Ser | Tyr  | Thr Arg | Val Pro | Pro  | Leu Val | Trp |  |
| 2405    |         |         | 2410 |         |         | 2415 |         |     |  |
| Lys Leu | Gly Trp | Ser Pro | Lys  | Pro Gly | Gly Asp | Phe  | Gly Thr | Ala |  |
| 2420    |         |         | 2425 |         |         | 2430 |         |     |  |
| Phe Pro | Glu Ile | Pro Val | Glu  | Phe Leu | Gln Glu | Lys  | Glu Val | Phe |  |
| 2435    |         |         | 2440 |         |         | 2445 |         |     |  |
| Lys Glu | Phe Ile | Tyr Arg | Ile  | Asn Thr | Leu Gly | Trp  | Thr Ser | Arg |  |
| 2450    |         |         | 2455 |         |         | 2460 |         |     |  |
| Thr Gln | Phe Glu | Glu Thr | Trp  | Ala Thr | Leu Leu | Gly  | Val Leu | Val |  |
| 2465    |         |         | 2470 |         |         | 2475 |         |     |  |
| Thr Gln | Pro Leu | Val Met | Glu  | Gln Glu | Glu Ser | Pro  | Pro Glu | Glu |  |
| 2480    |         |         | 2485 |         |         | 2490 |         |     |  |
| Asp Thr | Glu Arg | Thr Gln | Ile  | Asn Val | Leu Ala | Val  | Gln Ala | Ile |  |
| 2495    |         |         | 2500 |         |         | 2505 |         |     |  |
| Thr Ser | Leu Val | Leu Ser | Ala  | Met Thr | Val Pro | Val  | Ala Gly | Asn |  |
| 2510    |         |         | 2515 |         |         | 2520 |         |     |  |
| Pro Ala | Val Ser | Cys Leu | Glu  | Gln Gln | Pro Arg | Asn  | Lys Pro | Leu |  |
| 2525    |         |         | 2530 |         |         | 2535 |         |     |  |
| Lys Ala | Leu Asp | Thr Arg | Phe  | Gly Arg | Lys Leu | Ser  | Ile Ile | Arg |  |
| 2540    |         |         | 2545 |         |         | 2550 |         |     |  |
| Gly Ile | Val Glu | Gln Glu | Ile  | Gln Ala | Met Val | Ser  | Lys Arg | Glu |  |
| 2555    |         |         | 2560 |         |         | 2565 |         |     |  |
| Asn Ile | Ala Thr | His His | Leu  | Tyr Gln | Ala Trp | Asp  | Pro Val | Pro |  |
| 2570    |         |         | 2575 |         |         | 2580 |         |     |  |
| Ser Leu | Ser Pro | Ala Thr | Thr  | Gly Ala | Leu Ile | Ser  | His Glu | Lys |  |
| 2585    |         |         | 2590 |         |         | 2595 |         |     |  |
| Leu Leu | Leu Gln | Ile Asn | Pro  | Glu Arg | Glu Leu | Gly  | Ser Met | Ser |  |
| 2600    |         |         | 2605 |         |         | 2610 |         |     |  |

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|         |                 |      |                 |      |             |
|---------|-----------------|------|-----------------|------|-------------|
| Tyr Lys | Leu Gly Gln Val | Ser  | Ile His Ser Val | Trp  | Leu Gly Asn |
| 2615    |                 | 2620 |                 | 2625 |             |
| Ser Ile | Thr Pro Leu Arg | Glu  | Glu Glu Trp Asp | Glu  | Glu Glu Glu |
| 2630    |                 | 2635 |                 | 2640 |             |
| Glu Glu | Ala Asp Ala Pro | Ala  | Pro Ser Ser Pro | Pro  | Thr Ser Pro |
| 2645    |                 | 2650 |                 | 2655 |             |
| Val Asn | Ser Arg Lys His | Arg  | Ala Gly Val Asp | Ile  | His Ser Cys |
| 2660    |                 | 2665 |                 | 2670 |             |
| Ser Gln | Phe Leu Leu Glu | Leu  | Tyr Ser Arg Trp | Ile  | Leu Pro Ser |
| 2675    |                 | 2680 |                 | 2685 |             |
| Ser Ser | Ala Arg Arg Thr | Pro  | Ala Ile Leu Ile | Ser  | Glu Val Val |
| 2690    |                 | 2695 |                 | 2700 |             |
| Arg Ser | Leu Leu Val Val | Ser  | Asp Leu Phe Thr | Glu  | Arg Asn Gln |
| 2705    |                 | 2710 |                 | 2715 |             |
| Phe Glu | Leu Met Tyr Val | Thr  | Leu Thr Glu Leu | Arg  | Arg Val His |
| 2720    |                 | 2725 |                 | 2730 |             |
| Pro Ser | Glu Asp Glu Ile | Leu  | Ala Gln Tyr Leu | Val  | Pro Ala Thr |
| 2735    |                 | 2740 |                 | 2745 |             |
| Cys Lys | Ala Ala Ala Val | Leu  | Gly Met Asp Lys | Ala  | Val Ala Glu |
| 2750    |                 | 2755 |                 | 2760 |             |
| Pro Val | Ser Arg Leu Leu | Glu  | Ser Thr Leu Arg | Ser  | Ser His Leu |
| 2765    |                 | 2770 |                 | 2775 |             |
| Pro Ser | Arg Val Gly Ala | Leu  | His Gly Val Leu | Tyr  | Val Leu Glu |
| 2780    |                 | 2785 |                 | 2790 |             |
| Cys Asp | Leu Leu Asp Asp | Thr  | Ala Lys Gln Leu | Ile  | Pro Val Ile |
| 2795    |                 | 2800 |                 | 2805 |             |
| Ser Asp | Tyr Leu Leu Ser | Asn  | Leu Lys Gly Ile | Ala  | His Cys Val |
| 2810    |                 | 2815 |                 | 2820 |             |
| Asn Ile | His Ser Gln Gln | His  | Val Leu Val Met | Cys  | Ala Thr Ala |
| 2825    |                 | 2830 |                 | 2835 |             |
| Phe Tyr | Leu Ile Glu Asn | Tyr  | Pro Leu Asp Val | Gly  | Pro Glu Phe |
| 2840    |                 | 2845 |                 | 2850 |             |
| Ser Ala | Ser Ile Ile Gln | Met  | Cys Gly Val Met | Leu  | Ser Gly Ser |
| 2855    |                 | 2860 |                 | 2865 |             |
| Glu Glu | Ser Thr Pro Ser | Ile  | Ile Tyr His Cys | Ala  | Leu Arg Gly |
| 2870    |                 | 2875 |                 | 2880 |             |
| Leu Glu | Arg Leu Leu Leu | Ser  | Glu Gln Leu Ser | Arg  | Leu Asp Ala |
| 2885    |                 | 2890 |                 | 2895 |             |
| Glu Ser | Leu Val Lys Leu | Ser  | Val Asp Arg Val | Asn  | Val His Ser |
| 2900    |                 | 2905 |                 | 2910 |             |
| Pro His | Arg Ala Met Ala | Ala  | Leu Gly Leu Met | Leu  | Thr Cys Met |
| 2915    |                 | 2920 |                 | 2925 |             |
| Tyr Thr | Gly Lys Glu Lys | Val  | Ser Pro Gly Arg | Thr  | Ser Asp Pro |
| 2930    |                 | 2935 |                 | 2940 |             |
| Asn Pro | Ala Ala Pro Asp | Ser  | Glu Ser Val Ile | Val  | Ala Met Glu |
| 2945    |                 | 2950 |                 | 2955 |             |
| Arg Val | Ser Val Leu Phe | Asp  | Arg Ile Arg Lys | Gly  | Phe Pro Cys |
| 2960    |                 | 2965 |                 | 2970 |             |
| Glu Ala | Arg Val Val Ala | Arg  | Ile Leu Pro Gln | Phe  | Leu Asp Asp |
| 2975    |                 | 2980 |                 | 2985 |             |
| Phe Phe | Pro Pro Gln Asp | Ile  | Met Asn Lys Val | Ile  | Gly Glu Phe |
| 2990    |                 | 2995 |                 | 3000 |             |
| Leu Ser | Asn Gln Gln Pro | Tyr  | Pro Gln Phe Met | Ala  | Thr Val Val |

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| 3005                                                                          | 3010 | 3015 |
|-------------------------------------------------------------------------------|------|------|
| Tyr Lys Val Phe Gln Thr Leu His Ser Thr Gly Gln Ser Ser Met<br>3020 3025 3030 |      |      |
| Val Arg Asp Trp Val Met Leu Ser Leu Ser Asn Phe Thr Gln Arg<br>3035 3040 3045 |      |      |
| Ala Pro Val Ala Met Ala Thr Trp Ser Leu Ser Cys Phe Phe Val<br>3050 3055 3060 |      |      |
| Ser Ala Ser Thr Ser Pro Trp Val Ala Ala Ile Leu Pro His Val<br>3065 3070 3075 |      |      |
| Ile Ser Arg Met Gly Lys Leu Glu Gln Val Asp Val Asn Leu Phe<br>3080 3085 3090 |      |      |
| Cys Leu Val Ala Thr Asp Phe Tyr Arg His Gln Ile Glu Glu Glu<br>3095 3100 3105 |      |      |
| Leu Asp Arg Arg Ala Phe Gln Ser Val Leu Glu Val Val Ala Ala<br>3110 3115 3120 |      |      |
| Pro Gly Ser Pro Tyr His Arg Leu Leu Thr Cys Leu Arg Asn Val<br>3125 3130 3135 |      |      |
| His Lys Val Thr Thr Cys<br>3140                                               |      |      |
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| <211> LENGTH: 3307                                                            |      |      |
| <212> TYPE: DNA                                                               |      |      |
| <213> ORGANISM: Homo Sapiens                                                  |      |      |
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| ctgctagtat ccttgaactt ggttcattga gtgttttacg ctgaacgata ccaaatgccc             | 180  |      |
| acaggcataa aaggccact acccaacacc aagacacagt tcttcattcc ctacaccata              | 240  |      |
| aagagtaaa gtatagcagt aagaggagag caaggtactc ctggtccacc aggccctgct              | 300  |      |
| ggacctcgag ggcacccagg tccttctgga ccaccaggaa aaccaggcta cggaaagtcct            | 360  |      |
| ggactccaag gagagccagg gttgccagga ccaccgggac catcagctgt agggaaacca             | 420  |      |
| ggtgtgccag gactcccagg aaaaccagga gagagaggac catatggacc aaaaggagat             | 480  |      |
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| ccggctggaa tttctgtgcc aggaaaacct ggacaacagg gaccacagg agcccagga               | 600  |      |
| cccaggggct ttcctggaga aaaggggtgca ccaggagtcc ctggtatgaa tggacagaaa            | 660  |      |
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| ggtcccacag gaccatctgg ccctcctgga gtgggaaaa gaggtgaaaa tggggttcca              | 780  |      |
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| aaaggcatcc cgggtagcca tgggtctcca ggccctaaag gtgagacagg gccagctggg             | 1200 |      |
| cctgcaggat accctggggc taagggtgaa aggggttccc ctgggtcaga tggaaaacca             | 1260 |      |
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ttcttattta gtaacacaa gtgtgattaa tttgatttct ttaattcctt attgaatctt 2940
atgtgatatg attttctgga ttacagaac attagcacat gtacctgtg cctccattc 3000
aagtgaagtt ataatttaca ctgagggtt caaaattcga ctagaagtgg agatatatta 3060
tttatttatg cactgtactg tatttttata ttgctgttta aaacttttaa gctgtgctc 3120
acttattaaa gcacaaaatg ttttaacct tcctatttta cgacgcaata aaataacatc 3180
aatagatttt taggtggaat taatttgaaa gcagcaattt gctgttctca accattcttt 3240
caaggctttt cattgttcaa agttaataaa aaagtaggac aataaagtga aaaaaaaaa 3300
aaaaaaa 3307

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<210> SEQ ID NO 59  
 <211> LENGTH: 680  
 <212> TYPE: PRT  
 <213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 59

Met Leu Pro Gln Ile Pro Phe Leu Leu Leu Val Ser Leu Asn Leu Val  
 1 5 10 15

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|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| His | Gly | Val | Phe | Tyr | Ala | Glu | Arg | Tyr | Gln | Met | Pro | Thr | Gly | Ile | Lys |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |
| Gly | Pro | Leu | Pro | Asn | Thr | Lys | Thr | Gln | Phe | Phe | Ile | Pro | Tyr | Thr | Ile |
|     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |
| Lys | Ser | Lys | Gly | Ile | Ala | Val | Arg | Gly | Glu | Gln | Gly | Thr | Pro | Gly | Pro |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |
| Pro | Gly | Pro | Ala | Gly | Pro | Arg | Gly | His | Pro | Gly | Pro | Ser | Gly | Pro | Pro |
| 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |
| Gly | Lys | Pro | Gly | Tyr | Gly | Ser | Pro | Gly | Leu | Gln | Gly | Glu | Pro | Gly | Leu |
|     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |
| Pro | Gly | Pro | Pro | Gly | Pro | Ser | Ala | Val | Gly | Lys | Pro | Gly | Val | Pro | Gly |
|     |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |
| Leu | Pro | Gly | Lys | Pro | Gly | Glu | Arg | Gly | Pro | Tyr | Gly | Pro | Lys | Gly | Asp |
|     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |
| Val | Gly | Pro | Ala | Gly | Leu | Pro | Gly | Pro | Arg | Gly | Pro | Pro | Gly | Pro | Pro |
|     |     | 130 |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |
| Gly | Ile | Pro | Gly | Pro | Ala | Gly | Ile | Ser | Val | Pro | Gly | Lys | Pro | Gly | Gln |
| 145 |     |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     | 160 |
| Gln | Gly | Pro | Thr | Gly | Ala | Pro | Gly | Pro | Arg | Gly | Phe | Pro | Gly | Glu | Lys |
|     |     |     |     | 165 |     |     |     |     | 170 |     |     |     |     | 175 |     |
| Gly | Ala | Pro | Gly | Val | Pro | Gly | Met | Asn | Gly | Gln | Lys | Gly | Glu | Met | Gly |
|     |     | 180 |     |     |     |     | 185 |     |     |     |     |     | 190 |     |     |
| Tyr | Gly | Ala | Pro | Gly | Arg | Pro | Gly | Glu | Arg | Gly | Leu | Pro | Gly | Pro | Gln |
|     |     | 195 |     |     |     | 200 |     |     |     |     |     | 205 |     |     |     |
| Gly | Pro | Thr | Gly | Pro | Ser | Gly | Pro | Pro | Gly | Val | Gly | Lys | Arg | Gly | Glu |
|     | 210 |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |
| Asn | Gly | Val | Pro | Gly | Gln | Pro | Gly | Ile | Lys | Gly | Asp | Arg | Gly | Phe | Pro |
| 225 |     |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |
| Gly | Glu | Met | Gly | Pro | Ile | Gly | Pro | Pro | Gly | Pro | Gln | Gly | Pro | Pro | Gly |
|     |     |     | 245 |     |     |     |     |     | 250 |     |     |     |     | 255 |     |
| Glu | Arg | Gly | Pro | Glu | Gly | Ile | Gly | Lys | Pro | Gly | Ala | Ala | Gly | Ala | Pro |
|     |     | 260 |     |     |     |     |     | 265 |     |     |     |     | 270 |     |     |
| Gly | Gln | Pro | Gly | Ile | Pro | Gly | Thr | Lys | Gly | Leu | Pro | Gly | Ala | Pro | Gly |
|     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |
| Ile | Ala | Gly | Pro | Pro | Gly | Pro | Pro | Gly | Phe | Gly | Lys | Pro | Gly | Leu | Pro |
|     |     | 290 |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |
| Gly | Leu | Lys | Gly | Glu | Arg | Gly | Pro | Ala | Gly | Leu | Pro | Gly | Gly | Pro | Gly |
| 305 |     |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |
| Ala | Lys | Gly | Glu | Gln | Gly | Pro | Ala | Gly | Leu | Pro | Gly | Lys | Pro | Gly | Leu |
|     |     |     | 325 |     |     |     |     |     | 330 |     |     |     |     | 335 |     |
| Thr | Gly | Pro | Pro | Gly | Asn | Met | Gly | Pro | Gln | Gly | Pro | Lys | Gly | Ile | Pro |
|     |     | 340 |     |     |     |     | 345 |     |     |     |     |     | 350 |     |     |
| Gly | Ser | His | Gly | Leu | Pro | Gly | Pro | Lys | Gly | Glu | Thr | Gly | Pro | Ala | Gly |
|     |     | 355 |     |     |     |     | 360 |     |     |     |     | 365 |     |     |     |
| Pro | Ala | Gly | Tyr | Pro | Gly | Ala | Lys | Gly | Glu | Arg | Gly | Ser | Pro | Gly | Ser |
|     | 370 |     |     |     |     | 375 |     |     |     |     | 380 |     |     |     |     |
| Asp | Gly | Lys | Pro | Gly | Tyr | Pro | Gly | Lys | Pro | Gly | Leu | Asp | Gly | Pro | Lys |
| 385 |     |     |     |     | 390 |     |     |     |     | 395 |     |     |     |     | 400 |
| Gly | Asn | Pro | Gly | Leu | Pro | Gly | Pro | Lys | Gly | Asp | Pro | Gly | Val | Gly | Gly |
|     |     |     | 405 |     |     |     |     |     | 410 |     |     |     |     | 415 |     |
| Pro | Pro | Gly | Leu | Pro | Gly | Pro | Val | Gly | Pro | Ala | Gly | Ala | Lys | Gly | Met |
|     |     |     | 420 |     |     |     |     | 425 |     |     |     |     | 430 |     |     |
| Pro | Gly | His | Asn | Gly | Glu | Ala | Gly | Pro | Arg | Gly | Ala | Pro | Gly | Ile | Pro |
|     |     | 435 |     |     |     |     | 440 |     |     |     |     |     | 445 |     |     |

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Gly Thr Arg Gly Pro Ile Gly Pro Pro Gly Ile Pro Gly Phe Pro Gly  
 450 455 460  
 Ser Lys Gly Asp Pro Gly Ser Pro Gly Pro Pro Gly Pro Ala Gly Ile  
 465 470 475 480  
 Ala Thr Lys Gly Leu Asn Gly Pro Thr Gly Pro Pro Gly Pro Pro Gly  
 485 490 495  
 Pro Arg Gly His Ser Gly Glu Pro Gly Leu Pro Gly Pro Pro Gly Pro  
 500 505 510  
 Pro Gly Pro Pro Gly Gln Ala Val Met Pro Glu Gly Phe Ile Lys Ala  
 515 520 525  
 Gly Gln Arg Pro Ser Leu Ser Gly Thr Pro Leu Val Ser Ala Asn Gln  
 530 535 540  
 Gly Val Thr Gly Met Pro Val Ser Ala Phe Thr Val Ile Leu Ser Lys  
 545 550 555 560  
 Ala Tyr Pro Ala Ile Gly Thr Pro Ile Pro Phe Asp Lys Ile Leu Tyr  
 565 570 575  
 Asn Arg Gln Gln His Tyr Asp Pro Arg Thr Gly Ile Phe Thr Cys Gln  
 580 585 590  
 Ile Pro Gly Ile Tyr Tyr Phe Ser Tyr His Val His Val Lys Gly Thr  
 595 600 605  
 His Val Trp Val Gly Leu Tyr Lys Asn Gly Thr Pro Val Met Tyr Thr  
 610 615 620  
 Tyr Asp Glu Tyr Thr Lys Gly Tyr Leu Asp Gln Ala Ser Gly Ser Ala  
 625 630 635 640  
 Ile Ile Asp Leu Thr Glu Asn Asp Gln Val Trp Leu Gln Leu Pro Asn  
 645 650 655  
 Ala Glu Ser Asn Gly Leu Tyr Ser Ser Glu Tyr Val His Ser Ser Phe  
 660 665 670  
 Ser Gly Phe Leu Val Ala Pro Met  
 675 680

<210> SEQ ID NO 60  
 <211> LENGTH: 2125  
 <212> TYPE: DNA  
 <213> ORGANISM: Porcine

<400> SEQUENCE: 60

accttctgca ttgctccctt gggcacagag gaggacacag tgagctggta ggacaccaac 60  
 tccaggagct cccaacatcc agaatccatc tgcaaacatg ctgccacaaa cagccctttt 120  
 gctgtgctga ttgtccttga acttggttca tggagtgttt tatactgagc aataccaaac 180  
 acctacaggc ataaaaggcc caccatccaa caccaaggca cagttcttca tccctacgc 240  
 cataaagagt aaaggtatat cactaagagg agagcaaggt attcccggtc caccaggccc 300  
 cgctggacca cgagggcacc caggtccatc tggaccccca ggaaaaccag gcttcggaag 360  
 ccctggaccc caaggacagc cagggtctgc aggaccacca ggaccatcag ccactgggaa 420  
 gccaggtttg ccaggacccc aaggaaaacc aggggagaga ggaccatatg gaccaaagg 480  
 agatatggga cgggctgtgt taccaggacc acggggccca ccagggccac ctggtatccc 540  
 cggcccggtt ggaatttctg ttacaggaaa acctggacaa cagggaactg caggagcccc 600  
 aggaccagg ggctttcctg gagaaaaggg tgcaccagga gtccctggta tcaatggaca 660  
 gaaaggggaa acgggatatg gtgctcctgg ccgcccaggt gacaggggcc ttccaggccc 720  
 ccagggccca atgggaccac ctggccctcc tggagtggga aagagagggg aaaatggggt 780

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tcccggacaa ccaggcatca aaggatgatcg gggcttttcca ggagaaagtg gaccggctgg 840
tccaccaggc ccccaaggtc ctccctgggga acaaggacga gaaggcattg gaaagccagg 900
agctcctgga gccgcaggcc agccagggct tccagggaca aaaggtcacc ccggggctcc 960
aggaatggct gggcctccag gggctcctgg ctttgggaaa ccaggcttgc caggcctgaa 1020
gggacaaaga ggtcctatag gccttcacag ggctccaggt gccaaagggg aacaaggccc 1080
ggcaggtcat cctggggaac caggtctgac tggacccctt ggaagtaggg gacccaagg 1140
accaaaaggc atcccaggca ataacggggt cccaggccct aagggtgaga tagggctggc 1200
tgggctgca ggattccctg gggctaaggg agaaggggc ccctccgggt tagatggaaa 1260
accagggtac ccaggagaac caggtctcaa tgggtccaag ggtacccag ggtacccgg 1320
cccaaaaggc gaccctggaa ttggaggacc tcttggtctc ccaggccctg tgggcccagc 1380
aggagctaag ggagtgcctg gacacaatgg tgaggctggg ccaagagggt ccctggaat 1440
accaggtacc agaggtccca tcgggccacc aggcattcca ggattccctg gctctaaagg 1500
ggatccagga aatccaggtc ctccctggtc agctggcata gcaactaagg gcctcaatgg 1560
accactggg ccaccagggc ctccaggacc aaaaggatcat gctggagagc ctggcctccc 1620
agggccccc gggcccccag gccctccagg ccaagcggtc caccccaag gctttgtaaa 1680
ggaaggacag agggcttttg ttagtgccaa ccagggagta acaggaatgc ctgtatctgc 1740
cttcaactgt attctctcca aagcttacc agctataggt gctcccatcc cctttgataa 1800
gattttatat aacgggcaac agcactatga cccaaaaact ggaatcttta cctgcaggat 1860
acctggaatc tattacttct ctaccacat tcacgtgaag gggacccatg cttgggtggg 1920
cctgtataaa aatggcacc ctgtcatgta cacctatgat gaatatgtca aaggctacct 1980
ggatcaggct tcaggagtg ccatccttga tctcacagat aatgaccagg tatggctcca 2040
gctgccaac gctgggtcga acgggctgta ctctctgag tacgtccact cctctttctc 2100
aggattccta gtggtccaa tgtga 2125

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<210> SEQ ID NO 61
<211> LENGTH: 675
<212> TYPE: PRT
<213> ORGANISM: Porcine

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<400> SEQUENCE: 61

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Met Leu Pro Gln Thr Ala Leu Leu Leu Leu Leu Ser Leu Asn Leu
1             5             10            15

Val His Gly Val Phe Tyr Thr Glu Gln Tyr Gln Thr Pro Thr Gly Ile
20            25            30

Lys Gly Pro Pro Ser Asn Thr Lys Ala Gln Phe Phe Ile Pro Tyr Ala
35            40            45

Ile Lys Ser Lys Gly Ile Ser Leu Arg Gly Glu Gln Gly Ile Pro Gly
50            55            60

Pro Pro Gly Pro Ala Gly Pro Arg Gly His Pro Gly Pro Ser Gly Pro
65            70            75            80

Pro Gly Lys Pro Gly Phe Gly Ser Pro Gly Pro Gln Gly Gln Pro Gly
85            90            95

Leu Pro Gly Pro Pro Gly Pro Ser Ala Thr Gly Lys Pro Gly Leu Pro
100           105           110

Gly Pro Gln Gly Lys Pro Gly Glu Arg Gly Pro Tyr Gly Pro Lys Gly
115           120           125

Asp Met Gly Pro Ala Gly Leu Pro Gly Pro Arg Gly Pro Pro Gly Pro
130           135           140

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|             |         |             |         |         |         |         |     |
|-------------|---------|-------------|---------|---------|---------|---------|-----|
| Pro Gly Ile | Pro Gly | Pro Ala Gly | Ile Ser | Val Thr | Gly Lys | Pro Gly |     |
| 145         |         | 150         |         | 155     |         | 160     |     |
| Gln Gln Gly | Pro Ala | Gly Ala     | Pro Gly | Pro Arg | Gly Phe | Pro Gly | Glu |
|             | 165     |             |         | 170     |         | 175     |     |
| Lys Gly Ala | Pro Gly | Val Pro     | Gly Ile | Asn Gly | Gln Lys | Gly Glu | Thr |
|             | 180     |             | 185     |         |         | 190     |     |
| Gly Tyr Gly | Ala Pro | Gly Arg     | Pro Gly | Asp Arg | Gly Leu | Pro Gly | Pro |
|             | 195     |             | 200     |         | 205     |         |     |
| Gln Gly Pro | Met Gly | Pro Pro     | Gly Pro | Pro Gly | Val Gly | Lys Arg | Gly |
|             | 210     |             | 215     |         | 220     |         |     |
| Glu Asn Gly | Phe Pro | Gly Gln     | Pro Gly | Ile Lys | Gly Asp | Arg Gly | Phe |
| 225         |         | 230         |         | 235     |         |         | 240 |
| Pro Gly Glu | Ser Gly | Pro Ala     | Gly Pro | Pro Gly | Pro Gln | Gly Pro | Pro |
|             | 245     |             |         | 250     |         | 255     |     |
| Gly Glu Gln | Gly Arg | Glu Gly     | Ile Gly | Lys Pro | Gly Ala | Pro Gly | Ala |
|             | 260     |             | 265     |         |         | 270     |     |
| Ala Gly Gln | Pro Gly | Leu Pro     | Gly Thr | Lys Gly | His Pro | Gly Ala | Pro |
|             | 275     |             | 280     |         | 285     |         |     |
| Gly Met Ala | Gly Pro | Pro Gly     | Ala Pro | Gly Phe | Gly Lys | Pro Gly | Leu |
|             | 290     |             | 295     |         | 300     |         |     |
| Pro Gly Leu | Lys Gly | Gln Arg     | Gly Pro | Ile Gly | Leu Pro | Gly Ala | Pro |
| 305         |         | 310         |         | 315     |         | 320     |     |
| Gly Ala Lys | Gly Glu | Gln Gly     | Pro Ala | Gly His | Pro Gly | Glu Pro | Gly |
|             | 325     |             |         | 330     |         | 335     |     |
| Leu Thr Gly | Pro Pro | Gly Ser     | Arg Gly | Pro Gln | Gly Pro | Lys Gly | Ile |
|             | 340     |             | 345     |         |         | 350     |     |
| Pro Gly Asn | Asn Gly | Val Pro     | Gly Pro | Lys Gly | Glu Ile | Gly Leu | Ala |
|             | 355     |             | 360     |         | 365     |         |     |
| Gly Pro Ala | Gly Phe | Pro Gly     | Ala Lys | Gly Glu | Arg Gly | Pro Ser | Gly |
|             | 370     |             | 375     |         | 380     |         |     |
| Leu Asp Gly | Lys Pro | Gly Tyr     | Pro Gly | Glu Pro | Gly Leu | Asn Gly | Pro |
| 385         |         | 390         |         | 395     |         | 400     |     |
| Lys Gly Asn | Pro Gly | Leu Pro     | Gly Pro | Lys Gly | Asp Pro | Gly Ile | Gly |
|             | 405     |             |         | 410     |         | 415     |     |
| Gly Pro Pro | Gly Leu | Pro Gly     | Pro Val | Gly Pro | Ala Gly | Ala Lys | Gly |
|             | 420     |             | 425     |         |         | 430     |     |
| Val Pro Gly | His Asn | Gly Glu     | Ala Gly | Pro Arg | Gly Ala | Pro Gly | Ile |
|             | 435     |             | 440     |         | 445     |         |     |
| Pro Gly Thr | Arg Gly | Pro Ile     | Gly Pro | Pro Gly | Ile Pro | Gly Phe | Pro |
|             | 450     |             | 455     |         | 460     |         |     |
| Gly Ser Lys | Gly Asp | Pro Gly     | Asn Pro | Gly Pro | Pro Gly | Pro Ala | Gly |
| 465         |         | 470         |         | 475     |         | 480     |     |
| Ile Ala Thr | Lys Gly | Leu Asn     | Gly Pro | Thr Gly | Pro Pro | Gly Pro | Pro |
|             | 485     |             |         | 490     |         | 495     |     |
| Gly Pro Lys | Gly His | Ala Gly     | Glu Pro | Gly Leu | Pro Gly | Pro Pro | Gly |
|             | 500     |             | 505     |         | 510     |         |     |
| Pro Pro Gly | Pro Pro | Gly Gln     | Ala Val | Pro Pro | Glu Gly | Phe Val | Lys |
|             | 515     |             | 520     |         | 525     |         |     |
| Glu Gly Gln | Arg Ala | Phe Val     | Ser Ala | Asn Gln | Gly Val | Thr Gly | Met |
|             | 530     |             | 535     |         | 540     |         |     |
| Pro Val Ser | Ala Phe | Thr Val     | Ile Leu | Ser Lys | Ala Tyr | Pro Ala | Ile |
| 545         |         | 550         |         | 555     |         | 560     |     |
| Gly Ala Pro | Ile Pro | Phe Asp     | Lys Ile | Leu Tyr | Asn Gly | Gln Gln | His |

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| 565 |     |     |     |     | 570 |     |     |     |     | 575 |     |     |     |     |     |  |  |  |  |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|--|--|--|
| Tyr | Asp | Pro | Lys | Thr | Gly | Ile | Phe | Thr | Cys | Arg | Ile | Pro | Gly | Ile | Tyr |  |  |  |  |
| 580 |     |     |     |     | 585 |     |     |     |     | 590 |     |     |     |     |     |  |  |  |  |
| Tyr | Phe | Ser | Tyr | His | Ile | His | Val | Lys | Gly | Thr | His | Ala | Trp | Val | Gly |  |  |  |  |
| 595 |     |     |     |     | 600 |     |     |     |     | 605 |     |     |     |     |     |  |  |  |  |
| Leu | Tyr | Lys | Asn | Gly | Thr | Pro | Val | Met | Tyr | Thr | Tyr | Asp | Glu | Tyr | Val |  |  |  |  |
| 610 |     |     |     |     | 615 |     |     |     |     | 620 |     |     |     |     |     |  |  |  |  |
| Lys | Gly | Tyr | Leu | Asp | Gln | Ala | Ser | Gly | Ser | Ala | Ile | Leu | Asp | Leu | Thr |  |  |  |  |
| 625 |     |     |     |     | 630 |     |     |     |     | 635 |     |     |     |     | 640 |  |  |  |  |
| Asp | Asn | Asp | Gln | Val | Trp | Leu | Gln | Leu | Pro | Asn | Ala | Gly | Ser | Asn | Gly |  |  |  |  |
| 645 |     |     |     |     | 650 |     |     |     |     | 655 |     |     |     |     |     |  |  |  |  |
| Leu | Tyr | Ser | Ser | Glu | Tyr | Val | His | Ser | Ser | Phe | Ser | Gly | Phe | Leu | Val |  |  |  |  |
| 660 |     |     |     |     | 665 |     |     |     |     | 670 |     |     |     |     |     |  |  |  |  |
| Ala | Pro | Met |     |     |     |     |     |     |     |     |     |     |     |     |     |  |  |  |  |
| 675 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |  |  |  |

<210> SEQ ID NO 62  
 <211> LENGTH: 19  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Primer

<400> SEQUENCE: 62

atggcgacga aggccgtgt

19

<210> SEQ ID NO 63  
 <211> LENGTH: 26  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Primer

<400> SEQUENCE: 63

ttactgggtg atcccaatta caccac

26

<210> SEQ ID NO 64  
 <211> LENGTH: 37  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Primer

<400> SEQUENCE: 64

gactgctggc aaagatcgtg tggccactgt gtacatc

37

<210> SEQ ID NO 65  
 <211> LENGTH: 37  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Primer

<400> SEQUENCE: 65

gatgtacaca gtggccacac gatctttgcc agcagtc

37

<210> SEQ ID NO 66  
 <211> LENGTH: 25  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Primer

<400> SEQUENCE: 66

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gtcggaaacag gagagcgcac gaggg 25

<210> SEQ ID NO 67  
<211> LENGTH: 23  
<212> TYPE: DNA  
<213> ORGANISM: Artificial  
<220> FEATURE:  
<223> OTHER INFORMATION: Primer

<400> SEQUENCE: 67

gggtgatggt tcacgtagtg ggc 23

<210> SEQ ID NO 68  
<211> LENGTH: 20  
<212> TYPE: DNA  
<213> ORGANISM: Artificial  
<220> FEATURE:  
<223> OTHER INFORMATION: Primer

<400> SEQUENCE: 68

gtctccacc c attgacgtc 20

<210> SEQ ID NO 69  
<211> LENGTH: 20  
<212> TYPE: DNA  
<213> ORGANISM: Artificial  
<220> FEATURE:  
<223> OTHER INFORMATION: Primer

<400> SEQUENCE: 69

ggatcggtcc cggtgtcttc 20

<210> SEQ ID NO 70  
<211> LENGTH: 21  
<212> TYPE: DNA  
<213> ORGANISM: Artificial  
<220> FEATURE:  
<223> OTHER INFORMATION: Primer

<400> SEQUENCE: 70

gctgtaccag tgcaggtcct c 21

<210> SEQ ID NO 71  
<211> LENGTH: 20  
<212> TYPE: DNA  
<213> ORGANISM: Artificial  
<220> FEATURE:  
<223> OTHER INFORMATION: Primer

<400> SEQUENCE: 71

ccattgtgcg gccaatgatg 20

<210> SEQ ID NO 72  
<211> LENGTH: 21  
<212> TYPE: DNA  
<213> ORGANISM: Artificial  
<220> FEATURE:  
<223> OTHER INFORMATION: Primer

<400> SEQUENCE: 72

ggatcaagag aggcacgttg g 21

<210> SEQ ID NO 73  
<211> LENGTH: 22  
<212> TYPE: DNA  
<213> ORGANISM: Artificial

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<220> FEATURE:  
<223> OTHER INFORMATION: Primer

<400> SEQUENCE: 73

ggcgatcaca gaatcttcga tg

22

<210> SEQ ID NO 74  
<211> LENGTH: 18  
<212> TYPE: DNA  
<213> ORGANISM: Artificial  
<220> FEATURE:  
<223> OTHER INFORMATION: Primer

<400> SEQUENCE: 74

caaagatggt gtggccac

18

<210> SEQ ID NO 75  
<211> LENGTH: 18  
<212> TYPE: DNA  
<213> ORGANISM: Artificial  
<220> FEATURE:  
<223> OTHER INFORMATION: Primer

<400> SEQUENCE: 75

caaagatcgt gtggccac

18

<210> SEQ ID NO 76  
<211> LENGTH: 20  
<212> TYPE: DNA  
<213> ORGANISM: Artificial  
<220> FEATURE:  
<223> OTHER INFORMATION: Primer

<400> SEQUENCE: 76

cgtccacca actaagaacg

20

<210> SEQ ID NO 77  
<211> LENGTH: 20  
<212> TYPE: DNA  
<213> ORGANISM: Artificial  
<220> FEATURE:  
<223> OTHER INFORMATION: Primer

<400> SEQUENCE: 77

ctcaacacgg gaaacctcac

20

<210> SEQ ID NO 78  
<211> LENGTH: 8  
<212> TYPE: DNA  
<213> ORGANISM: Artificial  
<220> FEATURE:  
<223> OTHER INFORMATION: Probe

<400> SEQUENCE: 78

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<220> FEATURE:  
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<400> SEQUENCE: 103

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19

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22

<210> SEQ ID NO 105  
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ccagcaaacy aagtgggccca ttg

24

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<220> FEATURE:  
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<400> SEQUENCE: 121

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21

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<400> SEQUENCE: 123

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<210> SEQ ID NO 124  
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cagatgtaga gctggtgggg agg 23

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<210> SEQ ID NO 153  
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<212> TYPE: DNA  
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<212> TYPE: DNA  
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<220> FEATURE:  
<223> OTHER INFORMATION: Primer  
  
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<211> LENGTH: 29  
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<220> FEATURE:  
<223> OTHER INFORMATION: Primer  
  
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tctctagatc acattggagc cactacgaa 29

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The invention claimed is:

1. A transgenic pig model for a hereditary neurodegenerative autosomal dominant disease, comprising a transgenic pig whose genome comprises a DNA sequence encoding a protein involved in the development of a hereditary neurodegenerative autosomal dominant disease, wherein the transgenic pig expresses the protein in nerve tissue and exhibits a reduction in the number of neurons in the nerve tissue and an accumulation of protein aggregates in the nerve tissue.

2. The pig model according to claim 1, wherein said hereditary neurodegenerative autosomal dominant disease is amyotrophic lateral sclerosis.

3. The pig model according to claim 1, wherein said hereditary neurodegenerative autosomal dominant disease is Alzheimer's Disease.

4. The pig model according to claim 1, wherein said hereditary neurodegenerative autosomal dominant disease is Parkinson's Disease.

5. The pig model according to claim 1, wherein said hereditary neurodegenerative autosomal dominant disease is a disease related to trinucleotide repeats.

6. The pig model according to claim 1, wherein said hereditary neurodegenerative autosomal dominant disease is Huntington's chorea.

7. The pig model according to claim 1, wherein said hereditary neurodegenerative autosomal dominant disease is dyschondroplasia.

8. The transgenic pig model according to claim 1 obtainable by a sperm mediated gene transfer method (SMGT) comprising the steps of:

- i) providing semen from a male pig,
- ii) providing a DNA sequence encoding a protein involved in the development of a hereditary neurodegenerative autosomal dominant disease, wherein the transgenic pig expresses the protein in nerve tissue and exhibits a reduction in the number of neurons in the nerve tissue and an accumulation of protein aggregates in the nerve tissue when the protein is expressed in said pig model,
- iii) contacting said semen and said genetic material,
- iv) fertilising an oocyte from a female pig with the semen and the genetic determinant, and
- v) incubating said fertilised oocyte under conditions allowing said fertilised oocyte to develop into said pig model.

9. A method for producing a transgenic pig model for a hereditary neurodegenerative autosomal dominant disease, comprising a transgenic pig whose genome comprises a DNA sequence encoding a protein involved in the development of a hereditary neurodegenerative autosomal dominant disease, wherein the transgenic pig expresses the protein in nerve tissue and exhibits a reduction in the number of neurons in the nerve tissue and an accumulation of protein aggregates in the nerve tissue, said method comprising the steps of:

- i) providing semen from a male pig,
- ii) providing a DNA sequence encoding a protein involved in the development of a hereditary neurodegenerative autosomal dominant disease,
- iii) contacting said semen and said DNA sequence,
- iv) fertilising an oocyte from a female pig with the semen and the genetic material, and
- v) incubating said fertilised oocyte under conditions allowing said fertilised oocyte to develop into said transgenic pig, wherein the transgenic pig expresses the protein in nerve tissue and exhibits a reduction in the number of neurons in the nerve tissue and an accumulation of protein aggregates in the nerve tissue.

10. The method of claim 9, wherein the step of contacting said semen and said genetic material occurs in a buffer com-

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position comprising (a) glucose and (b) a citrate salt and/or a bicarbonate salt, optionally in combination with (c) a compound capable of chelating divalent metal ions, and further optionally in combination with (d) Bovine Serum Albumin (BSA), including any combination of (a) and (b) with (c) or (d).

11. A method for evaluating the response of a therapeutical treatment of a hereditary disease, said method comprising the steps of:

- a. providing a transgenic pig model for a hereditary neurodegenerative autosomal dominant disease, comprising a transgenic pig whose genome comprises a DNA sequence encoding a protein involved in the development of a hereditary neurodegenerative autosomal dominant disease, wherein the transgenic pig expresses the protein in nerve tissue and exhibits a reduction in the number of neurons in the nerve tissue and an accumulation of protein aggregates in the nerve tissue,
- b. treating said pig with at least one pharmaceutical composition exerting an effect on the reduction in the number of neurons in the nerve tissue or the accumulation of protein aggregates in the nerve tissue, and
- c. evaluating the effect observed.

12. The method of claim 11 comprising the further step of advising on medical treatment based on the afore-mentioned observed effects.

13. A transgenic pig sperm cell comprising a DNA sequence encoding a protein involved in the development of a hereditary neurodegenerative autosomal dominant disease wherein said protein is expressed in nerve tissue and exhibits a reduction in the number of neurons in the nerve tissue and an accumulation of protein aggregates in the nerve tissue when expressed in a pig host organism.

14. The pig sperm cell according to claim 13, wherein the DNA sequence is of mammalian origin, including human origin or porcine origin.

15. A method for producing a transgenic pig sperm cell comprising a DNA sequence encoding a protein involved in the development of a hereditary neurodegenerative autosomal dominant disease, wherein said protein is expressed in nerve tissue and exhibits a reduction in the number of neurons in the nerve tissue and an accumulation of protein aggregates in the nerve tissue when expressed in a pig host organism, said method comprising the steps of:

- a. providing a pig sperm cell,
- b. providing a DNA sequence encoding a protein involved in the development of a hereditary neurodegenerative autosomal dominant disease wherein said protein is expressed in nerve tissue and exhibits a reduction in the number of neurons in the nerve tissue and an accumulation of protein aggregates in the nerve tissue when expressed in a pig host organism, and
- c. contacting said pig sperm cell and said DNA sequence, wherein said contacting results in the uptake of the DNA sequence into the pig sperm cell.

16. A method for fertilising an oocyte by sperm-mediated gene transfer, said method comprising the steps of providing a pig sperm cell according to claim 13, and introducing said pig sperm cell into the oocyte to be fertilised, wherein said disease is a protein conformation disease.

17. A method for fertilising an oocyte by sperm-mediated gene transfer, said method comprising the step of providing a composition comprising a pig sperm cell in combination with a DNA sequence encoding a protein involved in the development of an hereditary neurodegenerative autosomal dominant disease wherein said protein is expressed in nerve tissue and exhibits a reduction in the number of neurons in the nerve

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tissue and an accumulation of protein aggregates in the nerve tissue when expressed in a pig host organism.

18. A transgenic embryo obtained by fertilising an oocyte with a pig sperm cell comprising a DNA sequence encoding a protein involved in the development of a hereditary neurodegenerative autosomal dominant disease wherein said protein is expressed in nerve tissue and exhibits a reduction in the number of neurons in the nerve tissue and an accumulation of protein aggregates in the nerve tissue when expressed in a pig host organism.

19. A transgenic embryo obtained by fertilising an oocyte with a composition comprising a DNA sequence encoding a protein involved in the development of a hereditary neurodegenerative autosomal dominant disease, wherein said protein is expressed in nerve tissue and exhibits a reduction in the number of neurons in the nerve tissue and an accumulation of protein aggregates in the nerve tissue when expressed in a pig host organism.

20. A method for the cultivation and development of a transgenic embryo obtained by fertilising an oocyte with a pig sperm cell comprising a DNA sequence encoding a protein involved in the development of a hereditary neurodegenerative autosomal dominant disease, said method comprising the step of cultivating said embryo under conditions allowing the embryo to develop into a pig offspring expressing said protein in nerve tissue and exhibiting a reduction in the number of neurons in the nerve tissue and an accumulation of protein aggregates in the nerve tissue.

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21. A method for screening the efficacy of a pharmaceutical composition, said method comprising the steps of:

- a. providing a transgenic pig model for a hereditary neurodegenerative autosomal dominant disease, comprising a transgenic pig whose genome comprises a DNA sequence encoding a protein involved in the development of a hereditary neurodegenerative autosomal dominant disease, wherein the transgenic pig expresses the protein in nerve tissue and exhibits a reduction in the number of neurons in the nerve tissue and an accumulation of protein aggregates in the nerve tissue,
- b. expressing in said pig model said DNA sequence involved in the development of a hereditary neurodegenerative autosomal dominant disease,
- c. administering to said pig the pharmaceutical composition, the efficacy of which is to be evaluated, and
- d. evaluating the effect, if any, of the pharmaceutical composition on the reduction in the number of neurons in the nerve tissue or the accumulation of protein aggregates in the nerve tissue exerted by the DNA sequence when expressed in the pig model.

22. The pig model according to claim 1, wherein said DNA sequence is expressed in a transient manner.

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